Neuromodulation of cognitive-behavioral control

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Chapter One

Spontaneous eye blink rate as predictor of dopamine-related cognitive function—a review

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Abstract

An extensive body of research suggests that the spontaneous eye blink rate (EBR) is a non-invasive indirect marker of central dopamine (DA) function, with higher EBR predicting higher DA function. In the present review we provide a comprehensive overview of this literature. We broadly divide the available research in studies that aim to disentangle the dopaminergic underpinnings of EBR, investigate its utility in diagnosis of DA-related disorders and responsivity to drug treatment, and, lastly, investigate EBR as predictor of individual differences in DA-related cognitive performance. We conclude that (i) EBR can reflect both DA receptor subtype D1 and D2 activity, although baseline EBR might be most strongly related to the latter, (ii) EBR can predict hypo- and hyperdopaminergic activity as well as normalization of this activity following treatment, and (iii) EBR can reliably predict individual differences in performance on many cognitive tasks, in particular those related to reward-driven behavior and cognitive flexibility. In sum, this review establishes EBR as a useful predictor of DA in a wide variety of contexts.

Introduction

Decades of research show the spontaneous eye blink rate (EBR) is closely associated with central dopamine (DA) function, particularly in the striatum. Specifically, EBR tends to correlate positively with DA activity at rest, illustrated by the fact that reduced and increased activity due to drugs or disorders is associated with low and high EBR, respectively. As a non-invasive and easily-accessible measure, EBR can serve as a reliable albeit non-distinctive method of assessing DA function in humans and might be preferable to invasive and expensive techniques such as positron emission tomography (PET). Indeed, ever since its relation to DA was postulated (Stevens, 1978b), EBR has become a popular method of investigating DA in a variety of contexts. For example, EBR has been used to evaluate effects of dopaminergic drugs on DA function, explore the role of DA in psychiatric disorders, and investigate the effects of individual differences in DA function on cognitive performance. In the present summary review, we provide a comprehensive overview of the literature on EBR as predictor of DA function, focusing on pharmacological studies of EBR, baseline EBR in atypical and healthy populations, and, lastly, whether EBR predicts cognitive performance thought to depend on DA. Lastly, we discuss the different methodologies for EBR assessment and provide recommendations for future research. We hope this review informs future studies of the applicability of EBR to a variety of paradigms and its utility in clarifying cognitive research findings by distinguishing results of low, intermediate, and high blinkers.

Dopamine and eye blink rate

To understand the relation between EBR and DA-driven cognition, and to allow theory-driven predictions to be made for results with EBR, it is necessary to first consider the role of DA in neurophysiology and how this translates to cognition. DA exerts widespread, non-linear modulatory influences on both prefrontal cortex and striatum, allowing it to affect a wide range of processes (Nieoullon, 2002; Seamans & Yang, 2004). One characteristic role of DA is that its phasic (stimulus-driven) release in striatum codes a reward prediction

error (Hollerman & Schultz, 1998; Schultz, Dayan, & Montague, 1997), with bursts indicating an outcome better than expected (i.e. a positive error) and dips and pauses indicating an outcome worse than expected (i.e. a negative error) (Maia & Frank, 2011). On the other hand, tonic (background) DA level enhances signal-to-noise ratio of neural activity by suppressing spontaneous firing in neurons with low membrane potentials but enhancing task-dependent firing in neurons with high membrane potentials (Frank, 2005; Hernández-López, Bargas, Surmeier, Reyes, & Galarraga, 1997).

When considering the effects of DA on cognition it is important to distinguish between two of its receptor subtypes that can serve opposite functions, D1 and D2, although more exist. D1 and D2 receptors in prefrontal cortex have been proposed to drive a 'closed' vs. 'open' processing state that facilitates robust online maintenance and flexible updating (gating) of cognitive representations, respectively (Durstewitz & Seamans, 2008). Particularly relevant for the present review, other models have highlighted a role for D1 and D2 in the basal ganglia, where these receptor systems interact to form a DA-modulated decision threshold for selecting responses and updating representations in the cortex (Bahuguna, Aertsen, & Kumar, 2015; Frank & O'Reilly, 2006; Maia & Frank, 2011). Specifically, a D1-rich direct pathway in the basal ganglia provides a 'Go' signal that facilitates updating of representations and selection of the response under consideration in the cortex, while a D2-rich indirect pathway provides a 'NoGo' signal that suppresses competing responses and representations. Importantly, whereas DA has excitatory effects on D1-driven Go signals, it is inhibitory on D2-driven NoGo signals (Maia & Frank, 2011). As such, higher levels of DA (e.g. due to positive prediction errors) lower the decision threshold and promote gating by facilitating D1-driven Go signals and inhibiting the D2-driven NoGo pathway, whereas at lower levels (e.g. due to negative prediction errors) it reduces inhibition of D2-driven NoGo signals and thus facilitates response suppression and stability of cortical representations.

These models of dopaminergic modulation of the stability and flexibility of cortical representations offer an explanation of why DA tends to

follow an inverted-u-shaped association with performance on tasks requiring cognitive control rather than following a more-is-better principle (Cools & D'Esposito, 2011). Cognitive control is popularly defined as achieving a balance between the opposing demands of stable maintenance of task goals in the face of distractors and their flexible updating when situational demands have changed (Cools & D'Esposito, 2011). This suggests that too high levels of DA can facilitate gating up to a point where it becomes dysfunctional, resulting in heightened distractibility and impaired response inhibition because the decision threshold is set too low. Conversely, too little DA might raise the threshold to a point of inducing inflexibility and perseveration. Hence, a moderate DA level is associated with an optimal compromise between stability and flexibility, although lower or higher DA, e.g. due to genotypic variation, may confer benefits in situations that require more of the former or latter (Cools & D'Esposito, 2011).

The association between DA, its receptor subtypes and cognitive functions allows us to form predictions on how EBR could predict DA-driven cognition and behavior. Although studies reviewed below suggest EBR can reflect both drug-induced D1 and D2 activity, there is evidence that resting EBR is more strongly related to the D2 receptor system (Groman et al., 2014), perhaps due to increased sensitivity of D2 receptors to DA as compared to D1 (Frank & O'Reilly, 2006). Given that D2 receptors are reportedly up to 11 times as prevalent in the striatum than frontal cortex (Camps, Cortés, Gueye, Probst, & Palacios, 1989) and D2 may have stronger effects on the decision threshold in basal ganglia than D1 (Bahuguna et al., 2015), it is possible EBR primarily relates to cognitive function via D2-driven modulation of the decision threshold in the basal ganglia. A higher EBR, indicative of higher DA activity, should then be related to increased inhibition of the basal ganglia NoGo pathway and a consequently reduced decision threshold and facilitated gating. Indeed, studies on EBR and cognitive flexibility reviewed below support the idea that a higher EBR is associated with increased flexibility, albeit at the potential cost of increased distractibility.

One question remaining is *why* EBR reflects DA activity. Although the neural circuitry through which DA modulates EBR remains open to further investigation, one prime candidate is the spinal trigeminal complex, which has been proposed to play a direct role in the spontaneous blink generator circuit (Kaminer, Powers, Horn, Hui, & Evinger, 2011; Kaminer, Thakur, & Evinger, 2015). Crucially, there is evidence that the basal ganglia, via the superior colliculus and nucleus raphe magnus, can modulate input to and excitability of the trigeminal complex, thus providing a pathway through which DA could affect the trigeminal complex and, in turn, blinking (Basso & Evinger, 1996; Basso, Powers, & Evinger, 1996; Basso, Strecker, & Evinger, 1993; Evinger et al., 1993; Evinger, Sibony, Manning, & Fiero, 1988; Gnadt et al., 1997; Harper, Labuszewski, & Lidsky, 1979; Kimura, 1973; Labuszewski & Lidsky, 1979; Napolitano, Bonuccelli, & Rossi, 1997; Schicatano, Peshori, Gopalaswamy, Sahay, & Evinger, 2000). In particular, Kaminer et al. (2011) proposed that DA inhibits the trigeminal complex, via effects on the nucleus raphe magnus, which results in increased spontaneous blinking, thus offering a potential account for the relation between DA and EBR.

Overview

The present review will be structured as follows. First, to provide insight in the dopaminergic underpinnings of the spontaneous EBR, we summarize studies examining the effects of dopaminergic manipulations on EBR in non-human primates, rats, and humans. Second, to illustrate EBR's relation to and utility in distinguishing between varying levels of baseline DA function, we review studies that measured EBR in different human populations such as individuals with neurological or psychiatric disorders or history of drug use, different age groups, and gender. Third, to demonstrate the applicability to and usefulness in a variety of paradigms of cognitive research, we provide an overview of studies relating EBR of healthy humans in rest to their performance on cognitive tasks. Lastly, we discuss the different methodologies used to assess EBR and offer recommendations for future research.

We performed an electronic search for articles using the PubMed and Web of Science databases, using the following search terms: (eye blink OR eye-blink OR eyeblink OR blink) AND rate. After selecting articles based on the title and abstract's relevance to DA function, we performed a forward and backward citation search for additional articles. We included only articles written in English.

Effects of dopaminergic manipulations on eye blink rate

In this section we review studies on the effects of dopaminergic manipulations on EBR in non-human primates, rats, and healthy humans. In Table 1 and 2 an overview of the following studies is provided, listing all drug and dose combinations, the associated EBR change, sample size, and methodology for EBR assessment. Note that many studies do not report the statistical significance of the change in EBR for every drug and dose combination. To avoid reporting inaccurate information, we list the EBR change as "not available" (NA) when the statistical significance for the given drug and dose combination is not explicitly reported in the text, tables, or figures. When a drug is reported to alter EBR but the significant dose was not specified, we report the EBR change as not available but include in parentheses the direction of effect suggested in-text. We revisit this issue in the discussion.

Table 1. Overview of dopaminergic single-drug studies in non-human primates, rats, and healthy humans.

Drug	Dose	EBR	*N*	Recording method	Condition	Study
Non-human primates						
Non-selective DA agonist						
Apomorphine	0.01 mg/kg	=	4	Observation	In cage	Kleven and Koek 1996
	0.02 mg/kg	=	4	Observation	In cage	Karson et al. 1981c
	0.02-0.12 mg/kg	=	4	Observation	In cage	Karson et al. 1981b
	0.03 mg/kg	=	4	Video	Primary gaze	Kotani et al. 2016
	0.04 mg/kg	↑	4	Observation	In cage	Kleven and Koek 1996
	0.1-0.2 mg/kg	↑	5	Observation	In cage	Lawrence and Redmond Jr. 1991
	0.1-1.0 mg/kg	↑	4	Video	Primary gaze	Kotani et al. 2016
	0.15 mg/kg	↓	3	Video	Video watching	Baker et al. 2002
	0.16 mg/kg	↑	4	Observation	In cage	Kleven and Koek 1996
	0.18-0.24 mg/kg	↑	4	Observation	In cage	Karson et al. 1981b
	0.25 mg/kg	↑	8	Observation	In cage	Casey et al. 1980
	0.36 mg/kg	↑	4	Observation	In cage	Karson et al. 1981c
	0.45 mg/kg	↑	4	Observation	In cage	Karson et al. 1981c
Cocaine	0.16 mg/kg	=	4	Observation	In cage	Kleven and Koek 1996
	0.63-2.5 mg/kg	↓	4	Observation	In cage	Kleven and Koek 1996
d-amphetamine	0.01-0.16 mg/kg	=	4	Observation	In cage	Kleven and Koek 1996
GBR 12935	0.16-2.5 mg/kg	=	4	Observation	In cage	Kleven and Koek 1996
Methamphetamine	0.03-3.2 mg/kg	NA (↑)	4	Video	In chamber	Jutkiewicz and Bergman 2004
Methylphenidate	0.16-2.5 mg/kg	NA (↓)	4	Observation	In cage	Kleven and Koek 1996
PD 128907	0.01-0.04 mg/kg	=	3-4	Observation	In cage	Kleven and Koek 1996
	0.16 mg/kg	↑	3-4	Observation	In cage	Kleven and Koek 1996
	0.3-1.0 mg/kg	↓	4	Video	Primary gaze	Kotani et al. 2016
Non-selective DA antagonist						
MPTP	0.63-1.25 mg/kg	↓	12	Observation	In cage	Mavridis et al. 1991
	2.0 mg/kg	↓	11	Observation	In cage	Lawrence and Redmond Jr. 1991
D1 agonist						
A77636	0.005-0.5 mg/kg	NA (↑)	10	Video	In chamber	Groman et al. 2014
Dihydrexidine	0.3-2.0 mg/kg	↑	5	Observation	In cage	Elsworth et al. 1991
R-6Br-APB	0.001-0.3 mg/kg	NA (↑)	7	Video	In chamber	Jutkiewicz and Bergman 2004
SKF 38393	3.0-17.8 mg/kg	=	7	Video	In chamber	Jutkiewicz and Bergman 2004
	30.0 mg/kg	NA (↓)	7	Video	In chamber	Jutkiewicz and Bergman 2004
SKF 75670	0.16-0.63 mg/kg	↑	3-4	Observation	In cage	Kleven and Koek 1996
	2.5 mg/kg	=	2	Observation	In cage	Kleven and Koek 1996
SKF 77434	0.03-1.0 mg/kg	NA	4	Video	In chamber	Jutkiewicz and Bergman 2004
	3.0-10.0 mg/kg	NA (↑)	4	Video	In chamber	Jutkiewicz and Bergman 2004
	17.8 mg/kg	=	4	Video	In chamber	Jutkiewicz and Bergman 2004
SKF 81297	0.03-3.0 mg/kg	NA (↑)	7	Video	In chamber	Jutkiewicz and Bergman 2004
	0.16 mg/kg	=	3-4	Observation	In cage	Kleven and Koek 1996
	0.63-2.5 mg/kg	↑	3-4	Observation	In cage	Kleven and Koek 1996
	0.03-1.0 mg/kg	NA (↑)	9	Video	In chamber	Jutkiewicz and Bergman 2004

SKF 82958	0.1-0.3 mg/kg	↑	4	Video	Primary gaze	Kotani et al. 2016
	0.16 mg/kg	=	3-4	Observation	In cage	Kleven and Koek 1996
	0.63-2.5 mg/kg	↑	3-4	Observation	In cage	Kleven and Koek 1996
SKF 83959	0.001-3.0 mg/kg	NA (↑)	7	Video	In chamber	Jutkiewicz and Bergman 2004
D1 antagonist						
SCH 23390	0.01 mg/kg	=	5	Observation	In cage	Elsworth et al. 1991
	0.05-0.3 mg/kg	↓	4	Observation	NA	Lawrence et al. 1991
	0.3 mg/kg	↓	5	Observation	In cage	Elsworth et al. 1991
	1.0-10.0 mg/kg	=	2	Observation	NA	Lawrence et al. 1991
SCH 39166	0.01-0.1 mg/kg	NA (↓)	4	Video	In chamber	Jutkiewicz and Bergman 2004
	0.03-0.1 mg/kg	=	4	Video	Primary gaze	Kotani et al. 2016
D2 agonist						
3-PPP	0.16 mg/kg	=	3-4	Observation	In cage	Kleven and Koek 1996
	0.63-2.5 mg/kg	↑	3-4	Observation	In cage	Kleven and Koek 1996
Bromocriptine	NA	↑	4	Observation	In cage	Karson et al. 1981c
Naxagolide	0.0025 mg/kg	=	3-4	Observation	In cage	Kleven and Koek 1996
	0.01-0.04 mg/kg	↑	3-4	Observation	In cage	Kleven and Koek 1996
PHNO	0.001-0.01 mg/kg	↑	5	Observation	In cage	Elsworth et al. 1991
	0.001-0.01 mg/kg	↑	5	Observation	In cage	Lawrence and Redmond Jr. 1991
	0.001-0.03 mg/kg	NA (↑)	4	Video	In chamber	Jutkiewicz and Bergman 2004
	0.001-0.1 mg/kg	↓	4	Video	Primary gaze	Kotani et al. 2016
	0.005-0.5 mg/kg	NA (↑)	10	Video	In viewing chamber	Groman et al. 2014
PPHT	0.01 mg/kg	=	3-4	Observation	In cage	Kleven and Koek 1996
	0.04-0.16 mg/kg	↑	3-4	Observation	In cage	Kleven and Koek 1996
Quinelorane	0.003-0.1 mg/kg	NA (↑)	3	Video	In chamber	Jutkiewicz and Bergman 2004
Quinpirole	0.01-0.16 mg/kg	↑	3-4	Observation	In cage	Kleven and Koek 1996
Roxindole	0.01 mg/kg	=	3-4	Observation	In cage	Kleven and Koek 1996
	0.04-0.16 mg/kg	↑	3-4	Observation	In cage	Kleven and Koek 1996
SDZ 208912	0.16-0.63 mg/kg	=	3-4	Observation	In cage	Kleven and Koek 1996
	2.5 mg/kg	=	2	Observation	In cage	Kleven and Koek 1996
Terguride	0.01-2.5 mg/kg	=	3-4	Observation	In cage	Kleven and Koek 1996
D2 antagonist						
Haloperidol	0.03 mg/kg	=	4	Video	Primary gaze	Kotani et al. 2016
	1.0 mg/kg	↓	5	Observation	In cage	Lawrence and Redmond Jr. 1991
Remoxipride	1.0 mg/kg	=	5	Observation	In cage	Elsworth et al. 1991
Sulpiride	100.0 mg/kg	↓	5	Observation	In cage	Lawrence and Redmond Jr. 1991
D4 agonist						
A 412997	0.1-0.3 mg/kg	=	4	Video	Primary gaze	Kotani et al. 2016
PD 168077	1.0-3.0 mg/kg	=	4	Video	Primary gaze	Kotani et al. 2016

Rats						
Non-selective DA agonist						
Apomorphine	1.0 mg/kg	↑	3	EMG	In cage	Kaminer et al. 2011
Methamphetamine	0.3-10.0 mg/kg	=	5-7	Video	Primary gaze	Desai et al. 2007
	10.0 mg/kg	=	2	Video	Primary gaze	Desai et al. 2007
D1 agonist						
Fenoldopam	0.01-1.0 mg/kg	=	5-7	Video	Primary gaze	Desai et al. 2007
R-6Br-APB	0.001-0.03 mg/kg	=	5-7	Video	Primary gaze	Desai et al. 2007
	0.1 mg/kg	↑	5-7	Video	Primary gaze	Desai et al. 2007
	0.3 mg/kg	=	5-7	Video	Primary gaze	Desai et al. 2007
	1.0-3.0 mg/kg	↑	5-7	Video	Primary gaze	Desai et al. 2007
SKF 82958	0.01-0.03 mg/kg	=	5-7	Video	Primary gaze	Desai et al. 2007
	0.1-0.3 mg/kg	↑	5-7	Video	Primary gaze	Desai et al. 2007
	1.0-10.0 mg/kg	=	5-7	Video	Primary gaze	Desai et al. 2007
SKF 83959, MCL 202	0.01-1.0 mg/kg	=	5-7	Video	Primary gaze	Desai et al. 2007
SKF 83959, MCL 204, 207	0.01-3.0 mg/kg	=	5-7	Video	Primary gaze	Desai et al. 2007
SKF 83959, MCL 206	0.03-1.0 mg/kg	=	5-7	Video	Primary gaze	Desai et al. 2007
SKF 83959, MCL 209	0.03-0.3 mg/kg	=	5-7	Video	Primary gaze	Desai et al. 2007
	1.0-3.0 mg/kg	↑	5-7	Video	Primary gaze	Desai et al. 2007
D1 antagonist						
SCH 23390	0.01 mg/kg	=	5-7	Video	Primary gaze	Desai et al. 2007
	0.03 mg/kg	↓	5-7	Video	Primary gaze	Desai et al. 2007
	0.1 mg/kg	=	5-7	Video	Primary gaze	Desai et al. 2007
	0.3 mg/kg	↓	5-7	Video	Primary gaze	Desai et al. 2007
	1.0 mg/kg	=	5-7	Video	Primary gaze	Desai et al. 2007
D2 agonist						
PHNO	0.0003-0.03 mg/kg	=	5-7	Video	Primary gaze	Desai et al. 2007
D2 antagonist						
Haloperidol	0.1 mg/kg	↓	3	EMG	In cage	Kaminer et al 2011
Healthy adult humans						
Non-selective DA agonist						
Apomorphine	0.0005-0.002 mg/kg	↑	8	Video	NA	Blin et al. 1990
d-amphetamine	0.25 mg/kg	↑	11	Observation	Interview	Strakowski et al. 1996
		↑	11	Observation	Interview	Strakowski et al. 1998
L-dopa	250 mg	=	39	EOG	Primary gaze	Mohr et al. 2005
Venlafaxine	12.5-25 mg	=	16	EOG	Auditory oddball task	Semlitsch et al. 1993
	50 mg	↑	16	EOG	Auditory oddball task	Semlitsch et al. 1993

D2 agonist						
Bromocriptine	0.04-0.05 mg/kg	=	11	Video	Primary gaze	Depue et al. 1994
	2.5 mg	=	12	Video	Silence	Ebert et al. 1996
Cabergoline	1.25 mg	Low blinkers: ↑	27	EOG	Rest	Cavanagh et al. 2014
		High blinkers: ↓	27	EOG	Rest	Cavanagh et al. 2014
Lisuride	0.2 mg	=	12	EOG	Primary gaze	Van der Post et al. 2004
D2 antagonist						
Sulpiride	400 mg	=	12	EOG	Primary gaze	Van der Post et al. 2004

↓, decreased at $p < .05$; ↑, increased at $p < .05$; =, no difference; DA, dopamine; EBR, eye blink rate; EMG, electromyography; NA; not available
Arrows between brackets indicate direction of effect reported in text without reporting specific EBR values and corresponding significance levels

Table 2. Overview of dopaminergic drug interaction studies in non-human primates and rats.

Main drug	Main drug dose	Pretreatment drug	Pretreatment drug dose	EBR	*N*	Recording method	Condition	Study
Non-human primates								
Non-selective DA agonist								
Apomorphine	0.1 mg/kg	(D2-) Haloperidol	1.0 mg/kg	Decrease is prevented	4	Observation	In cage	Lawrence and Redmond Jr. 1991
	0.3 mg/kg	(D1-) SCH 39166	0.1 mg/kg	Increase is prevented	4	Video	Primary gaze	Kotani et al. 2016
		(D2-) Haloperidol	0.03 mg/kg	Increase is unaffected	4	Video	Primary gaze	Kotani et al. 2016
	0.36 mg/kg	(D2-) Haloperidol	1.0 mg/kg	Increase is prevented	4	Observation	In cage	Karson et al. 1981c
	0.45 mg/kg	(D2-) Sulpiride	10.0 mg/kg	Increase is smaller	4	Observation	In cage	Karson et al. 1981c
D1 agonist			20.0 mg/kg	Increase is prevented	4	Observation	In cage	Karson et al. 1981c
Dihydrexine	0.3 mg/kg	(D1-) SCH 23390	0.01 mg/kg	Increase is prevented	5	Observation	In cage	Elsworth et al. 1991
		(D2-) Remoxipride	1.0 mg/kg	Increase is unaffected	5	Observation	In cage	Elsworth et al. 1991
R-6-BR-APB	0.01-3.0 mg/kg	(D1+) SKF 83959	0.1-3.0 mg/kg	Increase is smaller	3	Video	In chamber	Jutkiewicz and Bergman 2004
	0.03-10.0 mg/kg	(D1-) SCH 39166	0.1-1.0 mg/kg	Increase is smaller	4	Video	In chamber	Jutkiewicz and Bergman 2004
SKF 81297	2.5 mg/kg	(DA+) Cocaine	0.16-0.25 mg/kg	Increase is unaffected	3	Observation	In cage	Kleven and Koek 1996
SKF 82958	0.03-0.1 mg/kg	(D2+) PHNO	0.003 mg/kg	Increase is larger	3	Video	In chamber	Jutkiewicz and Bergman 2004
	0.03-3.0 mg/kg	(D2-) Haloperidol	0.01-0.1 mg/kg	Increase is unaffected	4	Video	In chamber	Jutkiewicz and Bergman 2004
	0.3-1.0 mg/kg	(D2+) PHNO	0.003 mg/kg	Increase is smaller	3	Video	In chamber	Jutkiewicz and Bergman 2004
D2 agonist								
PHNO	0.001 mg/kg	(D1-) SCH 23390	0.01 mg/kg	Increase is unaffected	5	Observation	In cage	Elsworth et al. 1991
		(D2-) Remoxipride	1.0 mg/kg	Increase is prevented	5	Observation	In cage	Elsworth et al. 1991
		(D2-) Sulpiride	100.0 mg/kg	Increase is prevented	5	Observation	In cage	Lawrence and Redmond Jr. 1991
Rats								
D1 agonist								
SKF 82958	0.003-0.3 mg/kg	(D1+) SKF 83959, MCL 204, 207	1.0 mg/kg	Increase is unaffected	5-6	Video	Primary gaze	Desai et al. 2007
	0.01-1.0 mg/kg	(D1+) SKF 83959, MCL 206	1.0 mg/kg	Increase is smaller	5-6	Video	Primary gaze	Desai et al. 2007
	0.03-1.0 mg/kg	(D1-) SCH 23390	0.03 mg/kg	Increase is smaller	5-6	Video	Primary gaze	Desai et al. 2007

+, agonist; -, antagonist; DA, dopamine; NA; not available

Animal studies

Early studies investigating the role of DA in EBR showed administration of the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), which destroys DA synthesizing cells in the substantia nigra, markedly reduced blink rate in monkeys (Lawrence and Redmond Jr., 1991; Mavridis et al., 1991). In contrast, in monkeys and rats the administration of apomorphine, a non-selective DA agonist, induced transient increases in EBR that lasted approximately one hour (Casey et al., 1980; Kaminer et al., 2011; Karson et al., 1981b, 1981c; Kleven and Koek, 1996; Kotani et al., 2016; Lawrence and Redmond Jr., 1991). One study reported EBR in monkeys was reduced 90 minutes after administration of apomorphine (Baker, Radmanesh, & Abell, 2002), suggesting a potential biphasic effect on DA activity not reported elsewhere. Although these studies support a link between EBR and DA, the non-selective nature of MPTP and apomorphine's effect on DA receptors does not reveal whether particular receptor subtypes might play different roles in EBR. One study demonstrated apomorphine-induced increases in EBR are completely blocked by a selective D1 but not a D2 antagonist (Kotani et al., 2016) whereas another study showed the D2 antagonist sulpiride could block an apomorphine-induced increase in EBR (Karson, Staub, et al., 1981b). As the nullfinding by Kotani et al. is possibly explained by a too low dose of D2 antagonist (haloperidol, 0.03 mg/kg) in comparison with Karson et al.'s higher dose of the same drug (1.0 mg/kg), it seems like apomorphine-induced changes in EBR are mediated both by D1 and D2 receptors.

To disentangle the contributions of D1 and D2 to EBR, studies have employed agonists that more selectively target either subtype and, in doing so, have shown both can affect EBR. D1 agonists increase EBR in monkeys and rats (Desai, Neumeyer, Bergman, & Paronis, 2007; Elsworth et al., 1991; Groman et al., 2014; Jutkiewicz & Bergman, 2004; Kotani et al., 2016) and this increase is negated by pretreatment with D1 antagonists (Elsworth et al., 1991; Jutkiewicz & Bergman, 2004). Treatment with only D1 antagonists can decrease EBR (Desai et al., 2007; Jutkiewicz & Bergman, 2004; Lawrence, Redmond, Elsworth, Taylor, & Roth, 1991). Likewise, D2 agonists have been

shown to increase EBR, although only in monkeys (Elsworth et al., 1991; Groman et al., 2014; Jutkiewicz and Bergman, 2004; Karson et al., 1981c; Lawrence and Redmond Jr., 1991), and this increase can be reversed by pretreatment with D2 antagonists (Elsworth et al., 1991; Kaminer et al., 2011). As with D1, treatment with only D2 antagonists can decrease EBR (Kaminer et al., 2011; Lawrence and Redmond Jr., 1991). One study further demonstrated the stimulating effect of the D2 agonist (+)-4-propyl-9-hydroxynapthoxazine (PHNO) on EBR was moderated by D2 receptor availability in the striatum, with the drug having stronger effects on EBR with increasing availability (Groman et al., 2014). No such relationship was found for the D1 agonist A 77636 and D1 receptor availability. Notably, baseline EBR was positively related to D2 but not D1 receptor availability, raising the possibility baseline EBR is primarily D2-driven while D1-mediated influences are restricted to pharmacological conditions. This is potentially explained by the fact D2 receptors are more sensitive to DA than D1 (Frank & O'Reilly, 2006).

Moreover, there is evidence suggesting the effects of D1 and D2 receptors on EBR are at least partly independent. This was first demonstrated by Elsworth et al. (1991), who administered monkeys either a D1 or D2 agonist, with or without a D1 or D2 antagonist. They found the D1 agonist produced a dose-dependent increase in EBR and this could be blocked only by the D1 and not the D2 antagonist. Conversely, the D2 agonist produced a dose-dependent increase in EBR that could be blocked only by the D2 and not the D1 antagonist. Similarly, Jutkiewicz and Bergman (2004) showed several D1 agonists produced significant increases in EBR that could be blocked by a D1 but not a D2 antagonist. Of particular interest is their additional finding that a D2 agonist can attenuate D1 agonist-induced increases in EBR, suggesting, although the two receptor subtypes can independently modulate EBR, they might also inhibit each other (Jutkiewicz & Bergman, 2004).

While most studies have focused on D1 and D2, others have also examined the effects of direct agonists targeting D3-4 receptors, as well as indirect agonists such as cocaine and amphetamine. Kotani et al. (2016) found

that in monkeys a D2/D3 agonist reduced EBR, proposed to be caused by increased drowsiness, while D4 agonists did not affect EBR. The indirect agonist amphetamine has been shown to increase EBR (Jutkiewicz & Bergman, 2004), although other studies found no effect (Desai et al., 2007; Kleven & Koek, 1996). Even a decrease in EBR following administration of the indirect agonists cocaine or methylphenidate was found (Kleven & Koek, 1996).

Overall, evidence from animal studies converges on the idea that pharmacological activation of D1 or D2 receptors modulates EBR and these receptors do so at least partly independent. Further, baseline EBR in monkeys was associated with D2 but not D1 receptor availability, suggesting D2 receptors in particular are linked to resting EBR. This is perhaps because the D2 receptor has been suggested to be far more sensitive to low DA levels than the D1 receptor (Frank & O'Reilly, 2006).

To conclude this section, it should be noted not all results have been unequivocal and this might be attributable to different drug doses across studies. The D2 agonist PHNO has also been found to decrease instead of increase EBR in monkeys (Kotani et al., 2016), proposed to be due to increased drowsiness, while the same drug did not affect rats (Desai et al., 2007). The former is surprising because the used dose was comparable to studies reporting increased EBR, but the nullfinding in rats may be due to a too low drug dose (0.0003-0.03 mg/kg). Also contradictory is Kotani et al. (2016) did not find lower EBR in monkeys following administration of only a D1 or D2 antagonist, but this might be because their doses were lower (0.01-0.1 mg/kg) compared to other studies that did report significant reductions. Indeed, Elsworth et al. (1991) found significantly reduced EBR after 0.3 mg/kg of the D1 antagonist SCH 23390 but not after 0.01 mg/kg. In sum, although results vary according to specific drugs and doses, the majority of animal drug studies indicate stimulation of either D1 or D2 receptors increases EBR, whereas blocking these receptors can reduce it.

Healthy human studies

Pharmacological studies investigating EBR in humans are less numerous than those conducted with animals but they reveal a similar albeit more complex picture than discussed so far. Consistent with previous studies, in healthy humans the non-selective DA agonist apomorphine increased EBR (Blin, Masson, Azulay, Fondarai, & Serratrice, 1990) and the indirect agonist amphetamine increased EBR as well (Strakowski, Sax, Setters, & Keck, 1996; Strakowski & Sax, 1998). Repeated doses of amphetamine induced sensitization effects, i.e. increases in EBR were larger for subsequent doses. On the other hand, administration of DA's precursor L-dopa did not affect EBR (Mohr, Sándor, Landis, Fathi, & Brugger, 2005). The antidepressant venlafaxine, which has DA reuptake-inhibiting effects, increased EBR at a dose of 50 mg but not 12.5 or 25 mg, although these findings may be confounded as placebo intake also resulted in increased EBR (Semlitsch, Anderer, Saletu, Binder, & Decker, 1993).

Studies investigating the effect of selective DA agonists in healthy humans are few and have all focused on D2 receptors, with mixed results. The D2 agonist bromocriptine did not affect EBR (Depue, Luciana, Arbisi, Collins, & Leon, 1994; Ebert et al., 1996) and, similarly, van der Post et al. (2004) did not find significantly altered EBR following either lisuride or sulpiride, D2 agonist and antagonist respectively. However, Cavanagh et al. (2014) showed administration of cabergoline, a D2 agonist, increased EBR in individuals with low blink rates at baseline but decreased EBR in those with high baseline blink rates. This indicates baseline EBR, and presumably the associated DA level, can modulate the effect of DA manipulations on blinking. This in turn suggests the previously mentioned nullfindings might be due to not considering baseline EBR of participants. Although an alternative explanation for these mixed findings might simply be related to different efficacies and doses of the respective drugs, as each used a different drug, the idea of modulation by baseline DA level fits the inverted-u-shaped relation DA typically has with cognitive-behavioral performance (Cools & D'Esposito, 2011).

In sum, drug studies in humans are mostly in line with the findings from animal studies, but they indicate drug-effects on EBR may not be linear and instead depend on baseline characteristics.

Baseline eye blink rate in human populations

Whereas the studies reviewed so far demonstrated pharmacological manipulations of DA can affect EBR, the following studies suggest endogenous differences, that is inter-individual variability in DA can also be of influence. For example, individuals with a history of neurological or psychiatric disorders or chronic/recreational drug use (hereafter referred to as 'atypical populations') can exhibit altered EBR. Indeed, Boutros and Hatch (1988) argued increased EBR might be a general marker of psychiatric illness, although as reviewed below severely decreased blink rates may be just as relevant. Individual differences are also found in healthy populations and might depend on factors such as age, gender, and certain lifestyle-practices. In the following sections we first focus on EBR in atypical populations thought to suffer from dysregulated DA activity, after which we examine factors of potential influence in healthy humans. In Tables 3 and 4 an overview of the following studies on atypical and healthy populations is provided, respectively.

Table 3. Overview of studies on EBR in atypical populations.

Population	EBR (relative)	EBR (mean atypical)	EBR (mean control)	*N* (atypical)	*N* (control)	Recording method	Condition	Study
Neurologic disorders								
Acute stroke	=	19.1	17.3	211	30	Observation	Conversation	Anagnostou et al. 2012
ALS (familial)	↓	6 (median)	13 (median)	11	42	NA	Watching video	Byrne et al. 2013
ALS (sporadic)	=	10.7 (median)	13 (median)	42	42	NA	Watching video	Byrne et al. 2013
Epilepsy (complex partial)	=	8.1	9.5	30	61	Video	Listening	Caplan et al. 1998
	↓	10.8	13.9	30	61	Video	Conversation	Caplan et al. 1998
	↓	14.6	19.7	30	61	Video	Verbal recall	Caplan et al. 1998
Epilepsy (myoclonic)	NA	8.3	NA	7	NA	Observation	NA	Schelkunov et al. 1986
Epilepsy (temporal)	NA	10.9	NA	19	NA	Observation	NA	Schelkunov et al. 1986
Generalized dystonia	=	23	24	9	82	Observation	Interview	Karson et al. 1984b
	↑	36.9	11.3	14	156	Observation	Primary gaze	Deuschl and Goddemeier 1998
Huntington's disease	NA	NA	NA	9	30	EOG	Primary gaze and/or movement	Valade et al. 1984
	=	36	24	10	82	Observation	Interview	Karson et al. 1984b
	NA	40	12 (median)	1	6	Video	Rest	Xing et al. 2008
Mild cognitive impairment	↑	27.6	20.2	36	33	EOG	Rest	Ladas et al. 2014
Multiple systems atrophy	↓	8.1	16.5	30	20	SMART	Primary gaze	Bologna et al. 2014
Parkinson's disease	↓	2.4	10.7	20	41	Video	Reading	Fitzpatrick et al. 2012
	=	4.7 (median)	9.5 (median)	10	14	Search coil	Watching video	Korošec et al. 2006
	↓	5.1	27.1	17	16	Video	Conversation	Kimber and Thompson 2000
	↓	5.8	11.3	51	156	Observation	Primary gaze	Deuschl and Goddemeier 1998
	↓	6.3	11.6	55	40	Observation	Rest	Aksoy et al. 2014
	↓	6.4	19.7	16	15	SMART	Primary gaze	Bologna et al. 2012
	↓	7.0	18.4	20	41	Video	Watching video	Fitzpatrick et al. 2012
	↓	7.3	10.6	30	338	Observation	Rest	Chen et al. 2003
	↓	7.4	21.9	10	10	SMART	Primary gaze	Agostino et al. 2008
	↓	8.0	19.1	13	11	Observation	Primary gaze	Agostino et al. 1987
	↓	8.5	12.4	4	5	Observation	Conversation	Reddy et al. 2013
	↓	12	16	34	24	Observation	Conversation	Karson et al. 1982b
	↓	12	24	25	82	Observation	Conversation	Karson et al. 1984b
	=	12.5	15.7	10	10	Video	Primary gaze	Golbe et al. 1989
	↓	12.7	21.7	56	34	Video	Watching video	Tamer et al. 2005
	=	14.8	9.1	10	10	Video	Horizontal versions	Golbe et al. 1989
	↓	17.1	24.8	30	31	NA	NA	Biousse et al. 2004
	↓	18.0	34.4	20	41	Video	Conversation	Fitzpatrick et al. 2012

	↑	20.4 (median)	9.5 (median)	6	14	Search coil	Watching video	Korošec et al. 2006
	=	24.3	21.9	6	10	SMART	Primary gaze	Agostino et al. 2008
	↑	32	16	21	24	Observation	Interview	Karson et al. 1982b
	↑	52.8	27.1	8	16	Video	Conversation	Kimber and Thompson 2000
Progressive supranuclear palsy	↓	1.9	12.4	7	5	Observation	Interview	Reddy et al. 2013
	↓	3.0	15.7	38	10	Video	Primary gaze	Golbe et al. 1989
	↓	4	24	5	82	Observation	Conversation	Karson et al. 1984b
	=	5.3	9.1	38	10	Video	Horizontal versions	Golbe et al. 1989
	↓	5.9	22.4	11	10	SMART	Primary gaze	Bologna et al. 2009
Schizophrenia	↑	NA	NA	13	13	EOG	SPEM	Klein et al. 1993
	↑	NA (summer)	NA (summer)	21	40	NA	NA	Karson et al. 1984a
	=	NA (winter)	NA (winter)	34	42	NA	NA	Karson et al. 1984a
	=	7.3 (median)	8 (median)	40	33	Observation	Counting	Chen et al. 1996
	↓	8.0	15.2	20	23	Video	Interview	Mackintosh et al. 1983
	NA	9.8	NA	5	NA	Observation	NA	Schelkunov et al. 1986
	↑	13 (median)	8.4 (median)	40	33	Observation	Listening music	Chen et al. 1996
	↑	20.3	11.2	10	12	Observation	Primary gaze	Helms and Godwin 1985
	↑	22	14	40	34	Observation	Interview	Adamson 1995
	↑	25	16	75	94	Observation	Listening music	Chan et al. 2010
	↑	28	22	27	36	Observation	Interview	Karson et al. 1983
	↑	30	NA	41	81	Observation	Interview	Kleinman et al. 1984
	NA	30+	NA	23	NA	EOG	NA	Stevens 1978a
	↑	31	23	44	54	Observation	Interview	Karson et al. 1981a
	↑	34.9	22.3	47	29	EOG	SPEM	Mackert et al. 1988
	↑	49.9	26.2	23	35	EOG	Rest	Swarztrauber and Fujikawa 1998
	NA	60+	NA	17	NA	EOG	NA	Stevens 1978b
	=	62.0	44.9	6	16	EOG	Cognitive tasks	Swarztrauber and Fujikawa 1998
Traumatic brain injury	↓	10.3	12.4	26	24	Video	NA	Konrad et al. 2003
Neurodevelopmental disorders								
AD(H)D	=	NA	NA	11 (on Mph)	12	EOG	Primary gaze	Groen et al. 2015
	=	NA	NA	13 (off Mph)	12	EOG	Primary gaze	Groen et al. 2015
	=	NA	NA	16 (off Mph)	18	EOG	Attention task	Groen et al. 2015
	=	NA	NA	16 (on Mph)	18	EOG	Attention task	Groen et al. 2015
	=	NA	NA	18	25	EOG	NA	Tantillo et al. 2002
	=	5.9	7.2	9	61	Observation	Counting	Daugherty et al. 1993
	↓	9.2	12.4	29	24	Video	NA	Konrad et al. 2003
	=	16.1	16.2	9	61	Observation	Interview	Daugherty et al. 1993

AD(H)D + conduct disorder	=	7.4	7.2	11	15	Observation	Counting	Daugherty et al. 1993
	=	18.9	16.2	11	15	Observation	Interview	Daugherty et al. 1993
Autism	↑	13	6	15	52	Observation	Interview	Goldberg et al. 1987
Conduct disorder	=	6.4	7.2	8	15	Observation	Counting	Daugherty et al. 1993
	=	15.6	16.2	8	15	Observation	Interview	Daugherty et al. 1993
Gilles de la Tourette syndrome	↑	NA	NA	19	21	Eyetracking	Cognitive task	Tharp et al. 2015
	↑	NA	NA	19	21	Eyetracking	Primary gaze	Tharp et al. 2015
	NA	12	NA	9	NA	Video	Calculating	Karson et al. 1985
	=	13	13	9	49	Video	Reading	Karson et al. 1985
	=	20	19	9	49	Video	Silence	Karson et al. 1985
	NA	26.6	NA	14	NA	Observation	NA	Schelkunov et al. 1986
	↑	35.1	14.1	9	10	Video	Rest	Tulen et al. 1999
	=	40.7	25.2	9	10	Video	Conversation	Tulen et al. 1999
	↑	44.0	16.7	9	10	Video	Watching video	Tulen et al. 1999
I(D)D	↓	8.9	19.6	25	19	Video	Primary gaze	Lee et al. 2010
I(D)D + stereotypy	↓	4.4	19.6	8	19	Video	Primary gaze	Lee et al. 2010
Mental retardation	↓	4	6	34	52	Observation	Interview	Goldberg et al. 1987
	↓	7.0	16.0	15	7	Observation	NA	Roebel and MacLean, Jr. 2007
Stereotypy	↓	6.0	14.7	10 (men)	10 (men)	Observation	Facing mirror	Maclean, Jr. et al. 1985
	=	10.4	6.3	10 (women)	10 (women)	Observation	Facing mirror	Maclean, Jr. et al. 1985
Psychiatric disorders								
Anorexia nervosa	↑	20	11	20	16	EOG	Primary gaze	Barbato et al. 2006
Anxiety withdrawal disorder	=	6.3	7.2	12	15	Observation	Counting	Daugherty et al. 1993
	=	14.7	16.2	12	15	Observation	Interview	Daugherty et al. 1993
Major depression	=	2.3	5.1	12	12	Video	Reading	Ebert et al. 1996
	=	20.1	19.6	12	12	Video	Listening	Ebert et al. 1996
	=	23.8	18.4	12	12	Video	Silence	Ebert et al. 1996
	↑	25.9	15.2	28	23	Video	Interview	Mackintosh et al. 1983
	=	30.5	27.4	12	12	Video	Calculating	Ebert et al. 1996
Major depression (psychotic)	↑	NA	NA	59	30	EOG	Rest	Giedke and Heimann 1987
	=	8.6	11.2	8	12	Observation	Primary gaze	Helms and Godwin 1985
Panic disorder	↑	NA	NA	11	16	Video	Rest	Kojima et al. 2002
	↑	NA	NA	11	16	Video	Watching video	Kojima et al. 2002
Psychosis	↑	16	10	13	35	Observation	NA	Karson et al. 1986
	NA	27.1	NA	38	NA	Observation	Interview	Ostow and Ostow 1945
	NA	104	NA	1	NA	NA	Interview	Lovestone 1992
Seasonal affective disorder	=	15	15	19	18	EOG	Primary gaze	Barbato et al. 1993

	↑	20.3 (winter)	10 (winter)	17	9	EOG	Silence	Depue et al. 1990
	↑	22.3 (summer)	8.3 (summer)	11	5	EOG	Silence	Depue et al. 1990
	↑	23.1	10.4	4	4	EOG	Silence	Depue et al. 1988
Miscellaneous disorders								
Fragile X syndrome	=	8.4	7.1	6	6	Video	Intelligence test	Roberts et al. 2005
	↑	12.7	6.9	6	6	Video	Watching video	Roberts et al. 2005
Graves' orbitopathy	=	17.6	19.8	10	10	Search coil	Watching video	Garcia et al. 2011
Iron-deficienct anemia	↓	4.0	5.3	19	42	Video	Watching bubbles	Lozoff et al. 2010
Prader-Willi syndrome	NA	18.7	NA	16	NA	Video	Watching video	Holsen and Thompson 2004
Wilson's disease	NA	32	NA	1	NA	NA	NA	Verma et al. 2012
Drug use								
Alcohol abuse	=	NA	NA	11	15	Video	NA	Upadhyaya et al. 2003
Cannabis	↓	10.2	17.5	25	25	EOG	Primary gaze	Kowal et al. 2011
Cocaine (recreational)	↓	9.3	17.1	12	12	EOG	Primary gaze	Colzato et al. 2008b

↓, decreased at $p < .05$; ↑, increased at $p < .05$; =, no difference; AD(H)D, attention deficit (hyperactivity) disorder; ALS, amyotrophic lateral sclerosis; EBR, eye blink rate; EOG, electrooculography; I(D)D, intellectual (and developmental) disorder; Mph, methylphenidate; NA, not available; SMART, SMART analyzer motion system; SPEM, smooth pursuit eye movement

Atypical populations

One of the first disorders to be associated with altered EBR is Parkinson's disease (PD; Hall, 1945), a condition characterized by severe progressive loss of dopaminergic neurons in the striatum (Dauer & Przedborski, 2003). Consistent with a hypodopaminergic state, PD or related features are associated with reduced EBR (Agostino et al., 2008; Agostino, Berardelli, Cruccu, Stocchi, & Manfredi, 1987; Aksoy, Ortak, Kurt, Cevik, & Cevik, 2014; Biousse et al., 2004; Bologna et al., 2014; Bologna, Fasano, Modugno, Fabbrini, & Berardelli, 2012; Deuschl & Goddemeier, 1998; Fitzpatrick, Hohl, Silburn, O'Gorman, & Broadley, 2012; Karson, Burns, LeWitt, Foster, & Newman, 1984; Karson, LeWitt, Calne, & Wyatt, 1982; Kimber & Thompson, 2000; Korošec, Zidar, Reits, Evinger, & Vanderwerf, 2006; Reddy, Patel, Hodge, & Leavitt, 2013; Tamer, Melek, Duman, & Öksüz, 2005), although three studies found only a nonsignificant decrease (Chen, Chiang, Hsu, & Liu, 2003; Golbe, Davis, & Lepore, 1989; Korošec et al., 2006). In line with the progressive nature of PD, some reported EBR was more strongly reduced with increasing disease severity or duration (Aksoy et al., 2014; Karson, Burns, et al., 1984; Karson, LeWitt, et al., 1982; Tamer et al., 2005). Although a meta-analysis suggested this association to be not significant (Fitzpatrick et al., 2012), no data was reported and thus more research is required before drawing definitive conclusions. Consistent with the idea PD can be treated by DA-stimulating drugs, EBR typically increases following treatment (Agostino et al., 2008; Bologna et al., 2012; Karson, Burns, et al., 1984; Kimber & Thompson, 2000; Korsgaard, Noring, & Gerlach, 1984). Such treatment may also explain the existence of subgroups of patients with higher EBR than healthy controls (Karson, LeWitt, et al., 1982; Kimber & Thompson, 2000; Korošec et al., 2006). For instance, L-dopa is the most common drug for treating PD and its pulsatile, in contrast to continuous, stimulation of DA receptors can lead to dyskinesias (Thanvi, Lo, & Robinson, 2007), which may result in increased EBR. In patients with tardive dyskinesia the D2 antagonist sulpiride did not reduce blink rates despite slight increases in Parkinsonism in some patients (Casey, Gerlach, & Simmelsgaard, 1979), suggesting this side-

effect is not easily reversed. Despite these patients exhibiting dyskenisia, reduced EBR is considered characteristic of PD, leading to its common inclusion in both the diagnosis of the disorder, as well as assessment of patients' responses to drug treatment.

The second prominent disorder related to altered EBR is schizophrenia, which is linked to excessive DA activity in the striatum (Howes, McCutcheon, & Stone, 2015). Consistent with a hyperdopaminergic state, schizophrenia patients typically exhibit increased EBR (Adamson, 1995; Chen, Lam, Chen, & Nguyen, 1996; Helms & Godwin, 1985; Karson, Berman, Kleinman, & Karoum, 1984; Karson, Freed, Kleinman, Bigelow, & Wyatt, 1981; Karson et al., 1983; Kleinman et al., 1984; Mackert, Woyth, Flechtner, & Frick, 1988; Ostow & Ostow, 1945; Stevens, 1978b, 1978a; Swarztrauber & Fujikawa, 1998), although one study found increased EBR only after 3 years since the first episode (Chan et al., 2010), another found the increase was no longer significant once smoking behavior was controlled for (Klein, Andresen, & Thom, 1993), and one study found EBR was actually reduced in, perhaps due to antipsychotic treatment (Mackintosh, Kumar, & Kitamura, 1983). As in PD, EBR in schizophrenia is proposed to correlate with symptomology. Specifically, EBR has correlated positively with psychotic behavior (Owens, Harrison-Read, & Johnstone, 1994), negative symptoms (Chen et al., 1996), general psychopathology and disinhibition (Chan & Chen, 2004), as well as perseverative errors in the Wisconsin card sorting test (Chan et al., 2010), and risk of relapse (Chan et al., 2010; Hui et al., 2013). Again, EBR varied with drug treatment: DA antagonists reduce blink rate (Adamson, 1995; Karson, Freed, et al., 1981; Kleinman et al., 1984; Mackert et al., 1988), and this change can correlate with improvement in symptoms (Bartkó, Herczeg, & Zádor, 1990; Karson, Bigelow, Kleinman, Weinberger, & Wyatt, 1982) but baseline EBR itself did not predict response to treatment (Bartkó, Frecska, Horváth, Zádor, & Arató, 1990). In other drug studies, Lieberman et al. (1987) found methylphenidate (Ritalin) increased EBR in patients with schizophrenia. They also found larger increases predicted earlier relapse, suggesting a potential role for enhanced receptor sensitivity. Indeed, Strakowski et al. (1997) found

amphetamine increased EBR in patients with schizophrenia but, in contrast to studies in healthy humans, there were no sensitization effects for repeated doses, which was interpreted as the patients' receptors already being maximally sensitized. Lastly, one study found no change in the blink rate but reduced anxiety when the non-selective DA agonist apomorphine was administered (Ferrier, Johnstone, & Crow, 1984). To conclude, it is interesting schizophrenia is associated with an increase in D2 receptors (for a review, see Seeman, 2013) and, as previously discussed, D2 receptor availability correlated positively with EBR in monkeys at rest (Groman et al., 2014). Taken together, these findings suggest increased EBR in schizophrenic patients is D2-mediated.

EBR might also be altered in individuals not diagnosed with schizophrenia but who do exhibit psychotic behavior. Indeed, EBR was reported to be increased in an adult (Lovestone, 1992) and adolescents (Karson, Goldberg, & Leleszi, 1986) suffering from psychosis. In contrast, individuals suffering from psychotic depression did not differ from controls (Helms & Godwin, 1985), although one study that grouped a large variety of psychiatric disorders, amongst others psychotic depression, bipolar affective disorder, and atypical psychosis, did find increased EBR in this group relative to healthy controls (Swarztrauber & Fujikawa, 1998).

With respect to affective disorders, there is mixed evidence for elevated EBR. Although depression might be linked to reduced DA activity resulting in the characteristic inability to experience pleasure, compensatory mechanisms have been proposed such as upregulation of postsynaptic DA receptors and decreased DA transporter density that may account for increased DA transmission and/or sensitivity (Dunlop & Nemeroff, 2007). Consistent with these compensatory mechanisms, some have reported increased EBR in major depression (Giedke & Heimann, 1987; Mackintosh et al., 1983), but others found no difference as compared to controls (Ebert et al., 1996). EBR was also not associated with depressive symptomology in undergraduate students (Byrne, Norris, & Worthy, 2016), although this is perhaps because not all students demonstrated clinical levels of depression and symptoms were rated

only for the past seven days instead of a longer period of time. One study did find sleep deprivation increased EBR in depressed individuals, accompanied by an improvement in depressive state proportional to the increase in EBR (Ebert et al., 1996). With respect to a different affective disorder, there is evidence for elevated EBR in seasonal affective disorder (SAD), with one study reporting increased blink rate (Depue et al., 1990) and another reporting an increase that was reversed by light therapy (Depue, Iacono, Muir, & Arbisi, 1988). In contrast, Barbato et al. (1993) found no difference between SAD individuals and controls, although light therapy did reduce EBR in premenopausal women with SAD. Overall, these studies seem to point to increased blink rate in affective disorders, but inconsistent results prevent a conclusive answer. Perhaps more consistency might be obtained by associating EBR with specific depressive symptoms related to rather than a diagnosis that is likely to encompass a highly heterogeneous population.

There is also mixed evidence for increased EBR in individuals at risk for or having already developed Huntington's disease. Specifically, EBR was suggested to be increased in family members of patients (Valade, Davous, & Rondot, 1984) and in a child two years prior to developing Huntington's (Xing et al., 2008). However, Karson et al. (1984b) found only a nonsignificant increase. Notably, the latter study counted EBR during conversation, which is shown to be increased relative to rest (for a review, see Doughty, 2001), and this may have partially confounded the results. We come back to this point in the discussion. Lastly, for this disorder it is perhaps particularly important to distinguish between baseline blink rates in contrast to blinks made during ocular tasks such as smooth pursuit and saccade tasks, which have been shown to be abnormally high as a consequence of a form of ocular apraxia (Lasker & Zee, 1997) that might not necessarily reflect elevated DA levels. Future studies examining EBR of Huntington's patients in resting conditions might shed more light on the nature of blink rate abnormalities in this disorder and the relation to DA dysfunction.

Aside from the disorders discussed so far, EBR has also been examined to a lesser extent in other conditions. As the studies in each respective disorder

are not numerous, we summarize them here only briefly. First, although attention-deficit hyperactivity disorder (ADHD) is thought to be linked with reduced DA activity (del Campo, Chamberlain, Sahakian, & Robbins, 2011), evidence for lower EBR is inconsistent. Whereas Konrad et al. (2003) found decreased EBR in children with ADHD, others found no difference in ADHD, ADD, with/without conduct disorder (Daugherty, Quay, & Ramos, 1993; Groen, Börger, Koerts, Thome, & Tucha, 2015; Tantillo, Kesick, Hynd, & Dishman, 2002). One of these studies also found no difference in children with anxiety withdrawal disorder (Daugherty et al., 1993). Second, EBR was increased in women with restricting type anorexia nervosa and their blink rate correlated positively with the duration of illness (Barbato, Fichele, Senatore, Casiello, & Muscettola, 2006), although it should be noted this difference is potentially driven by the healthy control group in this study having a rather low EBR (11 p/min). Third, EBR is typically increased in Tourette's syndrome, (Schelkunov, Kenunen, Pushkov, & Charitonov, 1986; Tharp et al., 2015; Tulen et al., 1999) and although one study (Karson, Kaufmann, Shapiro, & Shapiro, 1985) found no difference, they and others (Tulen et al., 1999) did find EBR correlated with the frequency of tics. Further, whereas the non-selective DA antagonist pimozide did not affect blink rate in this patients (Karson et al., 1985), the alpha-adrenergic agonist clonidine did reduce it (Cohen, Detlor, Young, & Shaywitz, 1980). Fourth, there is mixed evidence for altered EBR in generalized dystonia, with one study finding an increase (Deuschl & Goddemeier, 1998) and another finding no difference with controls (Karson, Burns, et al., 1984). Fifth, blink rate is reduced in individuals exhibiting stereotypic behavior (Lee et al., 2010; MacLean Jr. et al., 1985; Roebel and MacLean Jr., 2007) and the severity of repetitive behavior has correlated negatively with blink rate (Bodfish, Powell, Golden, & Lewis, 1995). Sixth, mild cognitive impairment was associated with increased EBR and these rates correlated negatively with Montreal cognitive assessment test scores (Ladas, Frantzidis, Bamidis, & Vivas, 2014). Seventh, EBR was increased in boys with fragile X syndrome and smaller changes in EBR from resting conditions to active cognitive tasks was associated with more problem

behavior (Roberts, Symons, Johnson, Hatton, & Boccia, 2005). Finally, EBR was increased in children with autism (Goldberg, Maltz, Bow, Karson, & Leleszi, 1987), in individuals with panic disorder (Kojima et al., 2002), progressive supranuclear palsy (Bologna et al., 2009, 2016; Golbe et al., 1989; Karson, Burns, et al., 1984; Reddy et al., 2013), Prader-Willi syndrome as compared to those with intellectual disability (Holsen & Thompson, 2004), and in a patient with Wilson disease (Verma, Lalla, & Patil, 2012). On the other hand, EBR was reduced in iron-deficient anemic infants (Lozoff et al., 2010), in children with traumatic brain injury (Konrad et al., 2003) or epilepsy (Caplan, Guthrie, Komo, & Shields, 1998; Schelkunov et al., 1986), and in patients with amyotrophic lateral sclerosis (ALS; Byrne et al., 2013), whereas there was no altered EBR in patients with Graves' orbitopathy (Garcia, Pinto, Barbosa, & Cruz, 2011), or cerebrovascular lesions (Anagnostou, Kouzi, Vassilopoulou, Paraskevas, & Spengos, 2012).

Lastly, altered baseline EBR is associated not only with the aforementioned disorders, but may stem from recreational drug use as well. Whereas alcohol abuse in adolescents was not associated with EBR (Upadhyaya et al., 2003), recreational use of cocaine in otherwise healthy adults was associated with reduced EBR as compared to matched cocaine-free controls, with the highest reported dosage ever taken correlating negatively with EBR (Colzato, van den Wildenberg, & Hommel, 2008). Similarly, Kowal et al. (2011) found reduced EBR in cannabis users that was correlated negatively with years of exposure, monthly peak consumption, and lifetime consumption.

In sum, EBR can reflect altered DA activity in various disorders as well as response to certain treatments, although the findings vary in consistency among disorders. Additionally, studies in drug users suggest chronic use of recreational DA drugs can result in hypodopaminergic activity that is reflected in reduced EBR.

Table 4. Overview of studies on EBR in relation to healthy inter-individual characteristics.

Factor	EBR	Mean EBR	*N*	Recording method	Condition	Study
Age						
NA	=	NA	NA	EOG	Primary gaze	Kruis et al. 2016
0.53 ± 0.29 years average	↑	3.6	64	Video	NA	Lawrenson et al. 2005
1 vs. 0.33 years	↑	NA vs. NA	87 vs. 98	Video	Auditory and visual stimulation	Bacher 2014
1 to 4 vs. 0 to 0.16 years	↑	3.4 vs. 0.7	54 vs. 14	Observation	Conversation	Zametkin et al. 1979
4.5 ± 0.31 years average	=	7.1	54	EOG	Watching video	Lackner et al. 2010
5 to 10 vs. 1 to 4 years	↑	6.1 vs. 3.4	96 vs. 54	Observation	Conversation	Zametkin et al. 1979
5.1 years vs. ≤ 30 days	↑	8.0 vs. 62	200 vs. 50	Video	Primary gaze	Lavezzo et al. 2008
11 to 15 vs. 5 to 10 years	↑	10.3 vs. 6.1	78 vs. 96	Observation	Conversation	Zametkin et al. 1979
15 to 20 vs. 11 to 15 years	=	11.3 vs. 10.3	23 vs. 78	Observation	Conversation	Zametkin et al. 1979
20 to 25 vs. 15 to 20	=	17.8 vs. 11.3	33 vs. 23	Observation	Sitting in waiting room or church	Zametkin et al. 1979
21.6 ± 1.47 years average	=	18.5	61	EOG	Primary gaze	Zhang et al. 2015
25 to 30 vs. 20 to 25	=	14.1 vs. 17.8	27 vs. 33	Observation	Sitting in waiting room or church	Zametkin et al. 1979
30 to 35 vs. 25 to 30	=	15.4 vs. 14.1	23 vs. 27	Observation	Sitting in waiting room or church	Zametkin et al. 1979
33.4 ± 7.0 years average	=	13.8	100	Video	Primary gaze	Doughty et al. 2006
35 to 40 vs. 30 to 35	=	16.3 vs. 15.4	20 vs. 23	Observation	Sitting in waiting room or church	Zametkin et al. 1979
35.9 ± 17.9 years average	=	17	150	Video	Rest	Bentivoglio et al. 1997
40 to 45 vs. 35 to 40	=	15.0 vs. 16.3	30 vs. 20	Observation	Sitting in waiting room or church	Zametkin et al. 1979
45 to 50 vs. 40 to 45	=	17.5 vs. 15.0	19 vs. 30	Observation	Sitting in waiting room or church	Zametkin et al. 1979
50 to 60 vs. 45 to 50	=	16.2 vs. 17.5	24 vs. 19	Observation	Sitting in waiting room or church	Zametkin et al. 1979
50.2 ± 17.0 years average	↓	10.6	338	Observation	Rest	Chen et al. 2003
57.1 years average	=	11.3	156	Observation	Primary gaze	Deuschl and Goddemeier 1998
59.3 vs. 23.9 years	=	16.9 vs. 12.9	19 vs. 25	SMART	Primary gaze	Sforza et al. 2008
60+ vs. 50 to 60	=	16.3 vs. 16.2	7 vs. 24	Observation	Sitting in waiting room or church	Zametkin et al. 1979
80 to 89 vs. 40 to 49 years	=	31.3 vs. 23.5	8 vs. 8	Video	Conversation	Sun et al. 1997
Birth control pill (yes vs. no)						
Women (yes) vs. women (no)	↑	19.6 vs. 14.9	44 vs. 42	Observation	Primary gaze	Yolton et al. 1994
Women (yes) vs. men	↑	19.6 vs. 14.5	44 vs. 59	Observation	Primary gaze	Yolton et al. 1994
Women (no) vs. men	=	14.9 vs. 14.5	42 vs. 59	Observation	Primary gaze	Yolton et al. 1994
Depressive symptomatology	=	17.8	104	EOG	Primary gaze	Byrne et al. 2016
Gender (women vs. men)	=	NA vs. NA	NA vs. NA	EOG	Primary gaze	Kruis et al. 2016
	=	NA vs. NA	NA vs. NA	Observation	Primary gaze	Deuschl and Goddemeier 1998
	=	NA vs. NA	NA vs. NA	Video	Watching video	Berenbaum and Williams 1994

	=	NA vs. NA	11 vs. 32	Video	Interview	Declerk et al. 2006
	=	NA vs. NA	20 vs. 7	EOG	Primary gaze	Colzato et al. 2009b
	=	NA vs. NA	20 vs. 21	EOG	Primary gaze	Di Gruttola et al. 2014
	=	NA vs. NA	30 vs. 31	EOG	Primary gaze	Zhang et al. 2015
	=	NA vs. NA	35 vs. 19	EOG	Watching video	Lackner et al. 2010
	↑	NA vs. NA	40 vs. 24	EOG	Rest	Dreisbach et al. 2005
	↑	NA vs. NA	74 vs. 18	EOG	Rest	Müller et al. 2007a
	=	1.2 vs. 1.3	26 vs. 26	Video	Listening music	Bacher and Allen 2009
	↑	5.4 vs. 3.9	39 vs. 35	Video	Auditory and visual stimulation	Bacher 2014
	↑	6.2 vs. 3.0	80 vs. 70	Video	Reading	Bentivoglio et al. 1997
	↓	6.3 vs. 14.7	10 vs. 10	Observation	Facing mirror	Maclean, Jr. et al. 1985
	=	9.7 vs. 10.8	31 vs. 30	Video	Primary gaze	Doughty 2002
	↓	9.8 vs. 11.4	173 vs. 165	Observation	Rest	Chen et al. 2003
	=	18 vs. 15.6	80 vs. 70	Video	Rest	Bentivoglio et al. 1997
	↑	19 vs. 11	21 vs. 23	SMART	Primary gaze	Sforza et al. 2008
	↑	19.5 vs. 15.9	54 vs. 50	EOG	Primary gaze	Byrne et al. 2016
	=	19.8 vs. 15.7	40 vs. 23	EOG	Primary gaze	Barbato et al. 2012
	↑	22.0 vs. 8.6	14 vs. 16	Video	Primary gaze	Pult et al. 2013
	=	26.7 vs. 24	80 vs. 70	Video	Conversation	Bentivoglio et al. 1997
Hypnotizability	↓	NA	36	NA	Watching light box	Lindsay et al. 1993
	↑	NA	41	EOG	Primary gaze	Di Gruttola et al. 2014
High vs. medium hypnotizability	↓	15.3 vs. 19.2	13 vs. 22	Video	Rest, conversation, listening music	Lichtenberg et al. 2008
Internal locus of control	↑	19.1	43	Video	Interview	Declerk et al. 2006
Meditation						
Long-term meditators vs. meditation-naïve controls	↓	NA vs. NA	27 vs. 118	EOG	Primary gaze	Kruis et al. 2016
Mindfulness-based stress reduction meditation pre vs. post	=	NA vs. NA	36	EOG	Primary gaze	Kruis et al. 2016
Mood						
Negative mood induction (post vs. pre)	=	16.8 vs. 17.4	38	EOG	Primary gaze	Akbari Chermahini and Hommel 2012
Positive affect	∩	NA	54	Video	Auditory and visual stimulation	Bacher 2014
Positive mood induction (post vs. pre)	↑	18.8 vs. 14.1	43	EOG	Primary gaze	Akbari Chermahini and Hommel 2012
Personality						
Extraversion	=	NA	51	Video	Primary gaze	Tharp and Pickering 2011
	=	NA	40 (men)	Video	Watching video	Berenbaum and Williams 1994
	↑	NA	34 (women)	Video	Watching video	Berenbaum and Williams 1994

	=	15.1	28	EOG	Primary gaze	Colzato et al. 2009a
	=	NA	39	NA	Flash detection	Franks 1963
	=	18.3	63	EOG	Primary gaze	Barbato et al. 2012
Neuroticism	=	NA	51	Video	Primary gaze	Tharp and Pickering 2011
	=	15.1	28	EOG	Primary gaze	Colzato et al. 2009a
	↑	18.3	63	EOG	Primary gaze	Barbato et al. 2012
Psychoticism	=	NA	51	Video	Primary gaze	Tharp and Pickering 2011
	↑	15.1	28	EOG	Primary gaze	Colzato et al. 2009a
	=	18.3	63	EOG	Primary gaze	Barbato et al. 2012
Lie	=	15.1	28	EOG	Primary gaze	Colzato et al. 2009a
Schizotypal thinking						
Negative schizotypy	=	9.9	21 (placebo)	EOG	Rest	Mohr et al. 2005
	↑	11.0	18 (L-dopa)	EOG	Rest	Mohr et al. 2005
Positive schizotypy	=	10.4	39	EOG	Rest	Mohr et al. 2005

↓, decreased at $p < .05$; ↑, increased at $p < .05$; ∩, inverted-u-curve at $p < .05$; =, no difference; EBR, eye blink rate; EOG, electrooculography; NA, not available;

Healthy populations

In healthy humans, the EBR has been suggested to vary according to several factors. First of all, EBR and age seem to follow a non-linear relation where EBR initially increases from infancy to adulthood (Bacher, 2014; Lavezzo, Schellini, Padovani, & Hirai, 2008; Lawrenson, Birhah, & Murphy, 2005; Zametkin, Stevens, & Pittman, 1979; Zhang et al., 2015), which is proposed to reflect maturation of the dopaminergic pathways (Lawrenson et al., 2005; Zametkin et al., 1979). From adulthood onwards, findings are less clear. EBR has been reported stable (Bentivoglio et al., 1997; Deuschl & Goddemeier, 1998; Doughty, 2006; Kruis, Slagter, Bachhuber, Davidson, & Lutz, 2016; Sforza, Rango, Galante, Bresolin, & Ferrario, 2008; Sun et al., 1997; Zametkin et al., 1979), while others found a decline from 40 onwards and in particular in women (Chen et al., 2003). Although an age-related decline in EBR would be consistent with the idea dopaminergic systems degrade with aging (Bäckman, Nyberg, Lindenberger, Li, & Farde, 2006), the evidence for such a decline remains inconsistent.

Second, there are equivocal findings on gender differences in blink rate. While several studies report no or marginal effects of gender (Bacher & Allen, 2009; Barbato, della Monica, Costanzo, & de Padova, 2012; Berenbaum & Williams, 1994; Colzato, van den Wildenberg, van Wouwe, Pannebakker, & Hommel, 2009; Declerck, de Brabander, & Boone, 2006; Deuschl & Goddemeier, 1998; Di Gruttola, Orsini, Carboncini, Rossi, & Santarcangelo, 2014; Doughty, 2002; Kruis et al., 2016; Lackner, Bowman, & Sabbagh, 2010; Yolton et al., 1994; Zametkin et al., 1979; Zhang et al., 2015), others find women blink more often than men (Bacher, 2014; Byrne et al., 2016; Dreisbach et al., 2005; Lozoff et al., 2010; Müller, Dreisbach, Brocke, et al., 2007; Pult, Riede-Pult, & Murphy, 2013; Sforza et al., 2008), although one study found this was only significant while reading and not at rest (Bentivoglio et al., 1997). Yet other studies report EBR to be lower in females (Chen et al., 2003; MacLean Jr. et al., 1985). Several accounts have been put forward to explain potential gender differences. For example, in infancy a higher EBR in females was proposed to reflect their faster maturation of dopaminergic

systems (Bacher, 2014). In adulthood, differences might arise from fluctuations in DA associated with the menstrual cycle, possibly due to estrogen. In line with this idea, D2 receptor availability varies according to the menstrual cycle (Czoty et al., 2009), cognitive functions associated with DA may depend on estrogen level (Colzato & Hommel, 2014; Jacobs & Esposito, 2011), oral contraceptives were found to increase EBR (Yolton et al., 1994), and a marked drop in EBR in older Chinese women was suggested to coincide with an age-related decrease in estrogen (Chen et al., 2003). Given the possible influence of different phases in the menstrual cycle on DA, future studies investigating gender effects on EBR should distinguish between women who do and do not take hormonal contraceptives and, in case of the latter, distinguish between participants in different phases of the menstrual cycle.

Third, EBR might correlate with certain dimensions of personality, although again there are inconsistent results that may partly be attributed to the different questionnaires used to measure personality. Extraversion measured using the Eysenck personality inventory (EPI) correlated positively in women but not men (Berenbaum & Williams, 1994), but did not correlate with either gender using the same questionnaire (Barbato et al., 2012), a short (Colzato, Slagter, van den Wildenberg, & Hommel, 2009) or longer version (Tharp & Pickering, 2011) of the Eysenck personality questionnaire revised short scale (EPQ-RSS), or the Maudsley personality inventory (Franks, 1963). Neuroticism correlated positively using the EPI (Barbato et al., 2012), but not the EPQ-RSS (Colzato, Slagter, et al., 2009; Tharp & Pickering, 2011). Psychoticism was found to positively correlate using the short (Colzato, Slagter, et al., 2009) but not longer (Tharp & Pickering, 2011) version of the EPQ-RSS or EPI (Barbato et al., 2012). The social conformity dimension 'lie' was not unrelated as measured using the EPQ-RSS (Colzato, Slagter, et al., 2009). Lastly, an internal locus of control correlated positively as measured using the Rotter internal-external control scale (Declerck et al., 2006). Overall, findings on EBR and personality have been inconsistent and future research should aim to replicate these findings across multiple independent studies and use different questionnaires in the same study for systematic comparison.

Fourth, there is inconclusive evidence for a correlation between EBR and schizotypal thinking (Mohr et al., 2005). EBR correlated positively with negative schizotypal thinking after administration of L-dopa (which did not significantly increase EBR), but not after a placebo. On the other hand, there was no relation with positive schizotypal thinking after either L-dopa or placebo intake.

Fifth, EBR has been proposed predict hypnotizability, which is thought to relate to DA (Lichtenberg et al., 2008). Whereas two studies found a negative correlation between EBR and hypnotizability (Lichtenberg et al., 2008; Lindsay, Kurtz, & Stern, 1993), one found a positive relation that disappeared once controlling for mind wandering (Di Gruttola et al., 2014). The authors of the latter study suggested differences in mind wandering might accounted for the inconsistency with previous studies. As such, future studies should aim to consider individual differences in mind wandering to provide a clear picture of the relation between EBR and hypnotizability.

Lastly, EBR was found to relate to the lifestyle practice meditation, consistent with the finding meditation affects DA-related cognitive functions (Kruis et al., 2016). While long-term meditators had lower EBR than meditation-naïve participants, there was no effect of an eight week course of mindfulness-based stress reduction nor of a full day of meditation practices on EBR. As such, it has been suggested pre-existing differences in DA might predispose an individual to practicing meditation, or meditation must be practiced on the long term for it to affect EBR.

Eye blink rate and cognitive performance in healthy humans

Consistent with the idea spontaneous EBR reflects striatal DA activity, many studies find EBR predicts DA-related cognitive performance. In the following section we review these studies to illustrate the applicability and usefulness of EBR in cognitive research. Most of the available research can be grouped in two broad categories, which are (i) reinforcement learning and motivation, that is learning from positive or negative outcomes of actions and the effort punt in and vigor of actions, and (ii) cognitive flexibility, i.e. updating of

representations in frontal cortex in contrast to their stable maintenance. After these two categories we summarize a number of other studies that do not fit these categories. In Table 5 an overview of the following studies is provided.

Table 5. Overview of studies on EBR in cognitive research.

Paradigm/Task	EBR	Mean EBR	N	Recording method	Condition	Study
Attentional blink in rapid serial visual presentation task	= with size of attentional blink	15.2	39	EOG	Primary gaze	Slagter and Georgopoulou 2013
	↓ with size of attentional blink	16.8	20	EOG	Primary gaze	Colzato et al. 2008a
	Binaural beats eliminated attentional blink in low but not high blinkers	17.4 (median)	24	EOG	Primary gaze	Reedijk et al. 2015
Cognitive flexibility						
Distractibility and perseveration in task-switching task	↑ with bias towards novel information	NA	50	Video	Primary gaze	Tharp and Pickering 2011
	↑ with bias towards novel information	NA	64	EOG	Rest	Dreisbach et al. 2005
	↑ with bias towards novel information	10.0	87	EOG	Rest	Müller et al. 2007a
	= with bias towards novel information	14.6	70	EOG	Primary gaze	Müller et al. 2007b
Divergent thinking in alternative uses task	∩ with flexibility scores	NA	117	EOG	Primary gaze	Akbari Chermahini and Hommel (2010)
	∩ with flexibility scores	15.8	81	EOG	Primary gaze	Akbari Chermahini and Hommel (2012)
	Binaural beats enhanced flexibility scores in low but not high blinkers	NA	24	EOG	Primary gaze	Reedijk et al. 2013
Task-switching in dots-triangles task	↑ with accuracy scores	18.5	61	EOG	Primary gaze	Zhang et al. 2015
	↓ with switch costs	18.5	61	EOG	Primary gaze	Zhang et al. 2015
Task-switching in local-global task	= with accuracy scores and switch costs	18.5	61	EOG	Primary gaze	Zhang et al. 2015
Convergent thinking in remote associations task	↓ with accuracy scores	NA	117	EOG	Primary gaze	Akbari Chermahini and Hommel (2010)
Ego-depletion induced by Stroop task	∩ with antisaccade performance after incongruent-only but not congruent-only Stroop task	NA	84	EOG	Primary gaze	Dang et al. 2016
Inhibitory control						
Impulsivity in distribution of attention	↑ with more impulsive distribution of attention, i.e. more fixation and longer dwell times on erotic pictures	12.7	50	Eyetracking	Primary gaze	den Daas et al. 2013
Response inhibition in go/no-go task	↑ with accuracy scores	18.5	61	EOG	Primary gaze	Zhang et al. 2015
Response inhibition in stop-signal task	↓ with latency of inhibitory control	14.0	27	EOG	Primary gaze	Colzato et al. 2009b
Response inhibition in Stroop task	= with accuracy scores in incongruent trials	18.5	61	EOG	Primary gaze	Zhang et al. 2015
	↓ with latency in incongruent trials	18.5	61	EOG	Primary gaze	Zhang et al. 2015
Motivation and effort in finger-tapping task	↑ with exerted effort (button presses) in response to suboptimal reward cues	18.9	36	Eyetracking	Primary gaze	Pas et al. 2014
Pseudoneglect in greyscales task	↑ with rightward bias in spatial attention	13.6	23	EOG	Primary gaze	Slagter et al. 2010
Reinforcement learning						

Loss aversion in Iowa gambling task	↑ with gains through enhanced loss aversion (for individuals with higher depressive symptomatology)	17.8	104	EOG	Primary gaze	Byrne et al. 2016
Punishment avoidance (conflict-induced) in Simon task	↑ with drug-induced bias towards conflict-induced punishment avoidance	NA	27	EOG	Rest	Cavanagh et al. 2014
Reinforcement learning in probabilistic reinforcement learning task	↓ with learning from negative outcomes	14.3	38	EOG	Primary gaze	Slagter et al. 2015
	= with learning from positive outcomes	14.3	38	EOG	Primary gaze	Slagter et al. 2015
Sense of agency in intentional binding paradigm	↑ with strength of intentional binding, (but only) when presented with positive pictures	15.8	28	Eyetracking	Primary gaze	Aarts et al. 2012
Theory of mind in false-belief task	↑ with theory of mind performance	7.2	54	EOG	Watching video	Lackner et al. 2010
Visuomotor binding in feature-repetition task	↑ with strength of visuomotor binding of task-relevant but not task-irrelevant features	8.7	18	EOG	Rest	Colzato et al. 2007a
Working memory						
Updating in mental counters task	= with accuracy scores	18.5	61	EOG	Primary gaze	Zhang et al. 2015
Updating in 3-back task	↓ with accuracy scores	18.5	61	EOG	Primary gaze	Zhang et al. 2015
Working memory span	= with working memory span	NA	50	Video	Primary gaze	Tharp and Pickering 2011

↓, decreased at $p < .05$; ↑, increased at $p < .05$; ∩, inverted-u-curve at $p < .05$; =, no difference; EBR, eye blink rate; EOG, electrooculography; NA, not available

Eye blink rate and reward-driven behavior

As indicated by the studies reviewed below, EBR can predict the effect of reinforcement learning on reward-driven task performance. This is consistent with the idea outlined in the introduction that EBR reflects activation of the D2 receptor system, which regulates the balance between positive reinforcement of behavior through Go learning and negative reinforcement through NoGo learning. Whereas the prediction errors driving such reinforcement learning depend on phasic (burst) DA release, background (tonic) DA level in the striatum is thought to be associated not with reward-driven learning per se but instead motivational aspects that determine the effort expended in and vigor of responding, as demonstrated in mice (Beeler, Daw, Frazier, & Zhuang, 2010; Niv, Daw, Joel, & Dayan, 2006) and humans (Treadway et al., 2012).

Evidence for an association between EBR and reinforcement learning comes from two studies that reveal EBR predicts learning from negative outcomes in particular. First, Slagter et al. (2015), using a probabilistic reinforcement learning task, found individuals with lower EBR tended to avoid choosing stimuli that were often unrewarded, but individuals with a higher EBR did not tend to choose regularly-rewarded stimuli more often. Consistent with these findings, Cavanagh et al. (2014) showed that pharmacologically reducing DA tone, as indicated by lower EBR, led to an increased aversion of punishment following response conflict. The authors administered low-dose cabergoline, which preferentially binds to D2 autoreceptors and thus reduces striatal DA release. Participants then performed a Simon task in which stimuli could lead to reward or punishment. Notably, for half of the stimuli the probability of reward and punishment was contingent on the congruency and thus associated conflict of the stimulus, although these stimuli were equally often rewarded. After completing the task, it was found lowering EBR increased the tendency to evaluate a stimulus whose incongruent trials always led to reward as being more rewarding than a stimulus whose incongruent trials never led to reward. Given that these stimuli was equally often rewarded, this finding suggests reduced striatal DA tone led to increasing the impact of punishment over reward.

The results of Slagter et al. (2015) and Cavanagh et al. (2014), showing a distinct relation of EBR with learning from negative versus positive outcomes, concur with the model for basal ganglia-mediated reinforcement learning as described in the introduction (Frank & O'Reilly, 2006; Maia & Frank, 2011). In this model a D1-rich direct pathway mediates Go learning driven by positive prediction errors (i.e. outcomes better than expected; reward) and a D2-rich indirect pathway mediates NoGo learning driven by negative prediction errors (i.e. outcomes worse than expected; punishment). Under the assumption EBR reflects D2 receptor function more than that of D1 (Groman et al., 2014) and given the D2-driven pathway mediates learning from negative outcomes (Maia & Frank, 2011), it is unsurprising lower EBR should predict learning from negative rather than positive outcomes. Although one might expect higher EBR to nevertheless promote learning from positive outcomes via stimulation of the D1/Go pathway and strengthened inhibition of the D2/NoGo pathway, this might not be the case because D2 receptors are more sensitive to DA than D1 (Frank & O'Reilly, 2006) and they have stronger inhibitory effects on the D1-driven pathway than vice versa (Bahuguna et al., 2015). As such, it might be DA levels in the healthy upper range are not high enough for sufficient stimulation of the D1 pathway to overcome its D2-driven inhibition, which would be consistent with the fact drug induced D1-activity affects EBR but D1 receptor availability is not related to resting EBR (Groman et al., 2014).

In apparent contrast to the findings of Slagter et al. and Cavanagh et al. is a study by Byrne et al. (2016), which investigated EBR and self-reported depressive symptomatology in undergraduate students in relation to performance on the Iowa gambling task (IGT). They found high but not low EBR, albeit combined with elevated depressive symptoms, was associated with increased loss-aversive behavior. Although a higher EBR was only marginally related to better IGT performance, i.e. making choices that lead to net gains, EBR and depressive symptomatology interacted such that individuals with more symptoms and high EBR performed better on the task. Modelling the data revealed having more depressive symptoms was associated with loss-

aversive behavior and individuals with high EBR persevered in choices that lead to net gains, speculated by the authors to be due to enhanced learning which options led to net losses and then avoiding those options.

These results contrast with those of Slagter et al. and Cavanagh et al. showing low instead of high EBR predicts aversion-avoidant behavior, as is expected from the basal ganglia Go/NoGo model. In light of these contradictory results it is important to consider two points on which these studies differed. First, Byrne et al. suggested differences in the format of the given reward may render these studies not comparable. Whereas Slagter et al. used the word 'Correct!' as a positive outcome and 'Incorrect' as a negative outcome, Cavanagh et al. used earning points as a reward and the absence of this reward as punishment, and Byrne et al. rewarded and punished participants by adding or subtracting points, respectively. Although these outcomes may be considered different based on the distinction in operant conditioning between 'positive' punishment by applying a stimulus vs. 'negative' punishment by removing a stimulus (Lieberman, 2000), both should lead to negative prediction errors (i.e. worse outcomes than expected) whose DA dips and pauses stimulate NoGo learning. Future studies might want to directly compare the relation between EBR and different forms of punishment in an attempt to resolve these inconsistent results. A second important difference is the results of Byrne et al. applied only to individuals who reported high depressive symptomatology, whereas no such distinction was made amongst the participants of Slagter et al and Cavanagh et al. Individuals with high depressive symptomatology might not be comparable to participants who did not report depressive symptoms, as processing of reward and punishment seems to be altered in depression (Ubl et al., 2015). Although highly speculative, perhaps Byrne et al.'s finding of increased loss-aversive behavior can be attributed not to DA but to a serotonin-mediated increase in learning of aversive outcomes that is associated with depression (Cools, Roberts, et al., 2008). On the other hand, the combination of high EBR and depressive symptoms, the latter possibly related to a compensatory increase in DA transmission (Dunlop & Nemeroff, 2007), may have led to sufficient D1

stimulation to account for the perseverative choosing of options leading to net gains. This explanation remains highly speculative and would require further investigation.

EBR has also predicted the amount of effort people are willing to spend on rewarded behavior. This was demonstrated by Pas et al. (2014), who showed EBR correlates positively with the amount of effort individuals exert in response to suboptimal reward cues. They used a finger-tapping task in which participants needed to carry out a high number of button presses in a short amount of time to earn money. The amount (low vs. high) was indicated at the beginning of a trial by a cue that could be considered optimal when presented supraliminal or suboptimal when presented subliminal through the use of masking. Consistent with the idea DA motivates reward-driven behavior, individuals with a higher EBR experienced a stronger reward effect for suboptimal cues. That is, the difference in exerted effort (button presses) between the two reward conditions (low and high) was larger for individuals with high EBR and this effect was only present for suboptimal cues. As such, this study indicates individuals with presumably higher striatal DA level exert more effort in reward-driven behavior under suboptimal conditions.

Further support for a role of DA in motivated behavior comes from a study by Aarts et al. (2012). They argued increasing DA activity could promote more motivated behavior and consequently increase the sense of agency over effects produced by this behavior. They measured sense of agency in the intentional binding paradigm, wherein increased sense of agency is indicated by stronger intentional binding. At the beginning of each trial participants saw either a neutral or positively valenced picture, the latter being considered rewarding and hence expected to induce phasic DA bursts. Results showed EBR was associated with stronger intentional binding, but only when positive but not neutral pictures were presented. Furthermore, positive pictures enhanced intentional binding in high but not low EBR individuals. These results suggest EBR is associated with motivated behavior but they also indicate it might be more accurate to say EBR modulates the effect of phasic DA bursts on motivated behavior.

Eye blink rate and cognitive flexibility

As discussed in the introduction, cognitive control benefits from a delicate balance between maintaining task-relevant representations in the face of interference and flexibly updating these representations when situational demands change (Cools & D'Esposito, 2011). DA gates the signal that elicits updating in frontal cortex by modulating the decision threshold in the basal ganglia such that a higher DA level facilitates updating by reducing the threshold (Frank & O'Reilly, 2006; Maia & Frank, 2011). In line with this model, the studies discussed below demonstrate EBR as indicator of DA level predicts task performance dependent on gating of representations.

A study by Zhang et al. (2015) demonstrated EBR can predict the efficiency of updating task-goal representations by showing high EBR was associated with increased accuracy and reduced switching costs. Although this result was obtained in a task in which participants needed to switch attending to dots and triangles, this was not replicated in a global-local task in which participants switch attending from larger, global stimuli to its comprising smaller, local stimuli. Curiously, scores on the two tasks did not correlate despite both presumably measuring task switching performance, suggesting certain differences between the tasks, e.g. level of difficulty, may have led to different associations with EBR. As such, this study suggests higher EBR, signaling a reduced threshold for updating task goals, predicts better cognitive flexibility performance but not in every kind of task.

Further support for a relation between EBR and cognitive flexibility comes from a series of studies showing high EBR is associated with improved task switching at the cost of increased distractibility, both being consistent with a reduced threshold for updating cortical representations in high EBR individuals. Dreisbach et al. (2005) had participants perform a classification task in which targets and distractors were signaled by different colors. When the target color switched to a novel one, higher EBR was associated with better performance, but performance worsened when the distractor rather than the target color became novel. This concurs with the idea higher EBR is associated with a reduced threshold for updating cortical representations, thereby

inducing a bias towards novel information that may or may not facilitate performance depending on the situational demands. These findings were replicated by Tharp and Pickering (2011) and Müller et al. (2007a), with the latter also finding this effect to be stronger in men than women. However, a follow-up study that adapted the paradigm to include reward found the effect of EBR was in the same direction but not statistically significant (Müller, Dreisbach, Goschke, et al., 2007). Although the authors proposed insufficient power as an explanation of this nullfinding, perhaps the presence of reward overshadowed the effect of color novelty in this task, leading to its weakened association with EBR. This nullfinding notwithstanding, the three studies that did report a significant effect confirm EBR predicts performance dependent on the updating of task goals.

In a different approach to cognitive flexibility, Akbari Chermahini and Hommel (2012, 2010) showed in several experiments EBR predicts divergent thinking, a crucial component of creativity thought to rely on the ability to flexibly switch between mindsets to generate many diverse ideas (Guilford, 1967). Given this description, divergent thinking would be expected to benefit from a reduced threshold for updating representations. Participants performed an alternative uses task (AUT) in which they need to list as many, preferably unconventional and original, uses for common household objects. The answers are rated, amongst others, according to how many different categories of uses are listed. This score, referred to as 'flexibility', was found to follow an inverted-u-shaped relation with EBR in each of four experiments. That is, scores were higher for intermediate blink rates and lower for low and high blink rates. Additionally, it was reported positive mood induction increased EBR and this was associated with enhanced flexibility scores but only for low-EBR individuals (Akbari Chermahini & Hommel, 2012). Furthermore, a follow-up study that also used the AUT found cognitive and neural entrainment through presentation of binaural beats could improve divergent thinking scores but only for individuals with a low EBR (Reedijk, Bolders, & Hommel, 2013), perhaps because they have most room for improvement. The AUT and EBR being non-linearly related suggests perhaps low blink rates are associated with

an inability to flexibly update the current category of use for the household item, whereas very high blink rates are associated with excessive triggering of categories inappropriate for the current item. Regardless, the fact EBR related to cognitively flexibility in a non-linear fashion is highly relevant for future studies on EBR, who need to consider not only linear correlations or median-split groups but quadratic relations as well.

Eye blink rate and other cognitive measures

Aside from the more-investigated topics of reward and cognitive flexibility, EBR has also been related to performance in a variety of other paradigms. In addition to task-switching as discussed in the previous section, two other key cognitive control processes are inhibitory control and (updating of) working memory (Miyake et al., 2000), both of which would require appropriate thresholding and gating for proper performance. Indeed, several studies indicate a relation between EBR, impulsivity, and inhibitory control, i.e. the ability to withhold prepotent responses, fitting the idea changes in the basal ganglia's response threshold affects the ability to inhibit responses. Colzato et al. (2009b) first showed EBR was related to inhibitory control as assessed in a stop-signal task, reporting higher EBR to be associated with increased latency of inhibitory processes, i.e. reduced inhibitory efficiency. Curiously, Zhang et al. (2015) found opposite results when using different tasks to measure inhibition. Using a go/no-go task, in which a go or no-go cue precedes an imperative go or no-go stimulus, they found EBR correlated positively with accuracy scores. They also found lower inhibition costs in a Stroop task, i.e. smaller differences in reaction time on incongruent as compared to congruent trials. In light of these contradictory findings it is interesting to note a study by den Daas et al. (2013) who investigated the relation between EBR and impulsivity as assessed through eye-tracking. The authors presented participants with side-by-side pictures of naked and clothed individuals and found high EBR individuals showed longer dwelling times and higher fixation counts on naked targets, which they interpreted as reflecting an impulsive state of attention distribution towards the most salient information. While this study

uses a very different methodology to assess inhibition, its findings are in line with Colzato et al. (2009b) to the extent that both show a high EBR predicts a reduced threshold for responding, either to the saliency of erotic pictures or an imperative stimulus.

Colzato et al.'s finding that higher EBR is associated with worse inhibitory control fits the idea higher striatal DA activity is associated with a reduced threshold for responding. Hence Zhang et al.'s finding that EBR was positively related with inhibitory performance in a go/no-go and Stroop task is striking. The Stroop result is especially surprising as EBR was previously associated with increased distractibility (Dreisbach et al., 2005; Müller, Dreisbach, Brocke, et al., 2007; Tharp & Pickering, 2011), suggesting higher EBR should impair performance in an incongruent Stroop condition in which semantic meaning is a salient distractor. Although Colzato et al. reported a lower mean EBR and less variation therein (M = 14.0, SD = 7.9) than Zhang et al. (M = 18.5, SD = 11.0), based on an inverted-u-shaped relation between EBR and inhibitory control this difference should have led Zhang et al. to find even larger impairments rather than improvements. This raises the possibility the inhibitory control processes tapped by the stop-signal task and go/no-go task are actually related to different optimal levels of DA and thus have different associations with EBR. This idea is tentatively supported by Fillmore et al. (2006), who found an inverted-u-shaped dose-response relationship between cocaine and stop-signal performance but a linear relationship between the same doses of cocaine in the same individuals and go/no-go performance. To validate this explanation future research should examine stop-signal and go/no-go performance in the same individuals in relation to EBR.

Zhang et al. (2015) also reported a relation between EBR and working memory, but only in one of two tasks. First, they found no effect in a mental counter task in which participants had to simultaneously keep track of the values of three independent counters that could each go up or down several times during a trial. However, they did find an effect in a visual, letter-based N-back task. The results showed a negative correlation between EBR and 3-back accuracy scores, indicating a lower threshold for updating information in

working memory led to levels of distractibility that impaired performance, consistent with the increased distractibility found in other studies (Dreisbach et al., 2005; Müller, Dreisbach, Brocke, et al., 2007; Tharp & Pickering, 2011). Given the characteristic inverted-u-shaped relation between DA and working memory (Cools & D'Esposito, 2011), it would be interesting to see whether future research can demonstrate a quadratic relation between EBR and *N*-back performance, perhaps by including a wider range of EBR values.

In one of the aforementioned studies on EBR and divergent thinking, another aspect of creativity was also examined (Akbari Chermahini & Hommel, 2010). This aspect is convergent thinking, which relies on finding the single correct answer for a constrained problem and as such requires narrow focus and online stabilization of task goals rather than flexible updating of representations. It was assessed using the remote associations task in which three unrelated words are shown and one must identify a single word that fits them all. Convergent thinking followed a negative linear correlation with EBR, but this effect was not very strong as it was only significant when data from three experiments was pooled. Although the mapping of convergent thinking on stability of representations versus divergent thinking on flexibility of representations is probably too restrictive to be completely accurate, these results fit the idea performance requiring a narrow focus and more stable representation of task goals suffers from an increased tendency to gate representations as indicated by higher EBR.

Recently, Dang et al. (2016) showed EBR might predict the ego-depletion effect on task performance. This effect refers to the idea exerting self-control depletes certain resources, which accounts for impaired self-regulation on a subsequent task (Baumeister, Bratslavsky, Muraven, & Tice, 1998). Participants completed either an easy, non-depleting version of the Stroop task consisting only of congruent trials, or a difficult, depleting version consisting only of incongruent trials. Subsequently, all participants completed an anti-saccade task in which strong attentional control is needed to prevent attention being drawn towards a distractor and away from a difficult-to-detect target. Hence this performance would be susceptible to depletion of self-

control. Contrary to their expectations, there was only an inverted-u-shaped relation between EBR and anti-saccade after the difficult, depleting version of the Stroop task but no association at all after completing the easy version of the Stroop task. Because a medium level of DA might be most beneficial to cognitive flexibility (Akbari Chermahini & Hommel, 2010, 2012), the authors argued participants with a medium EBR showed no cost from switching between the difficult Stroop and anti-saccade task, whereas those with a low or high EBR had less efficient task switching and thus performed worse on attentional control after a depleting task. In an attempt to validate this interpretation of the findings, future research could investigate an association between individual switching performance and the susceptibility to ego-depletion as measured by Dang et al. Until then, this study provides first, albeit tentative, evidence EBR can predict susceptibility to ego-depletion.

EBR has also been related to the attentional blink, which occurs when stimuli are presented in rapid succession and two to-be-detected stimuli are in close temporal proximity. Typical findings are the first target T1 is adequately detected but detection of the second target T2 is severely impaired when presented 200-500 ms after T1 (Raymond, Shapiro, & Arnell, 1992). One potential explanation for this phenomenon is T1 processing and consolidation in working memory occupies attentional mechanisms that are consequently unavailable when T2 follows shortly after T1 (Shapiro, 2001). Reasoning working memory is modulated by DA, Colzato et al. (2008a) found EBR predicts the size of the attentional blink. Specifically, individuals with a higher EBR had a smaller attention blink, i.e. better detection of T2. This suggests the reduced gating threshold in high EBR individuals may have facilitated the processing of T2 in frontal cortex, thereby increasing the odds participants are able to detect it. This effect was not replicated in a more recent study by Slagter and Georgopoulou (2013). Although this may have been due to technical differences such as stimulus duration and refresh rate of the computer screen, a probably more important difference is Colzato et al. used distractors and targets that were all colored black whereas Slagter and Georgopoulou used white distractors, a red T1, and a green T2. The latter methodology implies a

set switch between T1 and T2 is required, with participants needing to switch attending from the color red to green, which might introduce an additional bottleneck in the processing stream that masks individual differences in the attentional blink (Dale, Dux, & Arnell, 2013; Potter, Chun, Banks, & Muckenhoupt, 1998) and leads to a nonsignificant relationship with EBR. On a different topic, similar to a study on divergent thinking discussed above (Reedijk et al., 2013), binaural beats have been shown to completely eliminate the attentional blink but only in individuals with low EBR (Reedijk, Bolders, Colzato, & Hommel, 2015), again indicating a potential ceiling effect wherein high EBR individuals may not have enough room for improvement due to the binaural beats. Overall, these studies indicate a relation between EBR and the attentional blink but also highlight a need to consider experimental design choices (stimulus duration, presence of a set-switch between T1 and T2) that might affect the detectability of this relation.

Colzato et al. (2007a) found EBR can predict the strength of visuomotor binding, which is proposed to be driven by DA (Colzato, van Wouwe, & Hommel, 2007a). This was demonstrated using a task in which participants respond with a left or right keypress to stimuli with varying features (color, shape, location). Only one feature was responded to whereas the rest were irrelevant. Carrying out a response to a stimulus leads to concurrent activation of motor and sensory representations thought to result in bi-directional associations between motor and sensory representations, even those of task-irrelevant features, such that activation of either the motor or sensory code primes activation of the other (Hommel, 1998, 2004). Hence, in this task the repetition of a stimulus feature across trials can facilitate or impair the response to the current stimulus depending on whether its feature was previously associated with the correct or incorrect response on the current trial. The authors found individuals with a high EBR experienced greater impairment when feature-repetition primed an incorrect response, suggesting a stronger binding of response and sensory features in these individuals. Notably, this effect was restricted to repetition of the task-relevant feature, possibly due to a burst of DA triggered by the task-relevant feature leading this

feature to be processed more readily in prefrontal cortex, leading to its stronger binding with motor representations.

Interestingly, Slagter et al. (2010) showed EBR can predict individual differences in subtle biases in spatial attention. Such pseudoneglect is thought to be related to asymmetries of the DA system (Tomer, 2008). In particular, it is thought a high EBR might reflect higher activity in the left basal ganglia that leads to a contralateral, rightward shift in spatial attention (Slagter et al., 2010). This was confirmed using a greyscales task in which two black-to-white gradients are shown side by side, starting of as white in the middle and turning progressively darker towards the outer sides. Participants judged which of the two gradients was darker overall, although unbeknownst to them the gradients were identical in one condition of the task. As hypothesized, higher EBR was associated an increased tendency to judge the gradient on the right as darker. This finding confirms EBR can predict the direction of a subtle attentional bias and, perhaps more interestingly, this tentatively suggests a particular role of the left basal ganglia in EBR.

Lastly, a study by Lackner et al. (2010) showed EBR predicts representational theory of mind (RTM) performance in infants, which is consistent with a role for maturation of the DA system in theory of mind. Infants ranging from 4 to 6 years old performed a variety of RTM tasks, such as false-belief tasks that require them to consider others do not necessarily have access to the same information as they themselves do. As hypothesized, infants with higher EBR demonstrated more accurate performance, supporting the idea EBR in infants can reflect maturation of DA systems and development of RTM. This finding also concurs with the idea that if there is any relationship between EBR and age, it might be most pronounced and reliable in children (see section 3.2 on age and EBR).

Discussion

This review provided an overview of research on spontaneous EBR as indicator of DA function. Here we summarize the most important conclusions,

consider the different methodologies used to assess EBR, and give suggestions for future research.

The reviewed literature indicates, first of all, pharmacological activation of either D1 or D2 receptors can affect EBR, although baseline EBR seems positively related to availability of striatal D2 but not D1 receptors. As such, resting EBR might primarily reflect D2 receptor activity in the striatum, perhaps because D2 receptors are more sensitive to low DA levels than D1 receptors (Frank & O'Reilly, 2006). The reviewed cognitive literature supports this idea by showing EBR predicts learning mediated by the D2 receptor system in the basal ganglia, but not learning thought to be driven by D1 (e.g. Slagter et al., 2015). The drug literature also indicates the effects of drugs on DA activity and EBR are not always straightforward, as low and high-dose agonists might have opposite, counterintuitive effects on DA activity and EBR (Cavanagh et al., 2014; Frank & O'Reilly, 2006). Second, a large body of literature shows EBR can serve as a marker of DA function in neurological and psychiatric disorders or recreational drug users, reflecting dopaminergic hypo- or hyperactivity as well as response to drug treatment. Additionally, there is research suggesting EBR can co-vary with factors such as age, gender, and personality, although findings so far have been equivocal. In an attempt to provide more consistent results, future research should aim to use comparable measurement tools to assess personality across studies and distinguish between women in different phases of the menstrual cycle or taking hormonal contraceptives. Lastly, studies employing a variety of cognitive paradigms show EBR is a useful predictor of cognitive-behavioral performance. It appears most reliably related to reward-driven behavior and cognitive flexibility, consistent with the idea increased DA as reflected by higher EBR is accompanied by facilitated gating of cortical representations.

Methodologies of eye blink rate assessment

As revealed by the tables listed in this review, there is considerable variability in the methods used to record EBR and the conditions under which these recordings took place. It is important to consider these differences, as they may

contribute to variability in EBR data not related to DA. The most often-used recording methods are direct observation and counting by a researcher, and visual inspection of a video recording or electrooculography (EOG) measurement. Less-often used methods are magnetic search coils applied to the eyelid that produce a digitally-recorded current upon blinking, a SMART analyzer motion system that tracks a reflective marker taped on the eyelid, and eyetrackers for which signal loss lasting between 200 and 500 ms is considered a likely blink.

Each method may raise concerns, although none seem grave enough to warrant dismissal as for most concerns alleviating factors are proposed. That is not to say some methods might be best suited for different conditions or populations. For example, there is the possibility of human error or interrater differences when assessing EBR via direct observation or visual inspection of recordings and this might be especially problematic when for high EBR the blinks are difficult to visually separate (Zaman & Doughty, 1997). In these cases search coils, a SMART system, or EOG might be preferable for their ability to depict sensitive measurements of eyelid movement. A concern regarding search coils and reflecting markers from SMART may be that their placement on eyelids could affect blinking, but one study reported the coil did not impair eyelid movement and participants become unaware of its presence quickly (Garcia et al., 2011), whereas studies with SMART reported there are no adverse effects related to the experimental procedures (Bologna et al., 2014, 2012). The third alternative, which is by far the most often-used method in cognitive research, is EOG in which blinking results in a brief, high-amplitude shift of opposite polarity in signals recorded by electrodes positioned above and below the eyes (see Lackner et al. (2010) for a visual representation of blinks in EOG channels). This can provide a sensitive measure of muscle movement near the eyes, which also means movement of nearby muscles, e.g. from speaking, may create noise from which blinks are difficult to distinguish. The susceptibility of the EOG signal to participants' movements means this method may be best suited to conditions involving as little movement as possible and individuals/patients who are able to sit still. This ties into an

obvious caveat in studies estimating blinks as brief signal loss during eyetracking, which is many other events may account for such signal loss. Although these studies count only brief intervals of signal loss that befit the swift nature of blinking, this does not discount the possibility of technical issues nor the fact that individuals might exhibit movements that lead to signal loss without necessarily reflecting a blink. This might be especially relevant for movement disorders such as PD and tic behavior in Gilles de la Tourette. Nevertheless, eyetracking has provided theory-driven findings with EBR in healthy adults (Aarts et al., 2012; den Daas et al., 2013; Pas et al., 2014), tentatively suggesting this method produces reliable measurements under the right circumstances.

Another highly variable factor in methodology is the duration of recordings, which range from a single minute to an hour or longer. If reliable estimates of EBR are to be obtained in only a few minutes, as most studies attempt, it is important blinking behavior is stable throughout this period. However, as noted by Doughty (2016) reports on this stability have been mixed, with some indicating increasing variability throughout the measurement period or starting after three minutes (Depue et al., 1990; Doughty, 2013, 2014; Zaman & Doughty, 1997). Such claims raise concern about the reliability of brief measurements. However, Doughty (2016) found EBR variability to be stable when measuring the first 35 blinks during a maximum of 5 minutes. Importantly, this only applied when participants maintained primary gaze, i.e. looking straight ahead at a fixation point, whereas variability fluctuated significantly if a chin support was used. Although these results support the idea short measurements can result in reliable estimates, they also indicate variability in EBR can be determined in part by the recording methodology. This calls for more systematic studies to reveal how conditions other than primary gaze can be adjusted to allow reliable brief measurements. Related to this point, Doughty (2016) notes some studies advocate for an initial adjustment period of several minutes for participants to acclimate to the recording room, but more research is necessary to

systematically investigate the potential effect of different adjustment periods on (variability in) EBR.

With respect to the conditions under which EBR has been measured, it is important to acknowledge a distinction between two types of EBR that may have different relations with DA. On the one hand there is 'tonic' EBR, referring to baseline rates of blinking at rest, and 'phasic' EBR, referring to blink rates in response to stimulus conditions (Bacher & Allen, 2009). Tonic EBR is typically assessed in primary gaze, that is by having subjects not perform any kind of task and instead look straight ahead at a neutral, white wall or fixation point, whereas phasic EBR is assessed while subjects for example watch a video, read, or converse. The distinction between tonic and phasic EBR is important because numerous activities alter EBR relative to rest, thereby limiting the comparability of results acquired under different conditions. For example, reading and conversing reduce and increase EBR, respectively (for a review, see Doughty, 2001), and increased mental workload and task difficulty reduce EBR (for a review, see Lean & Shan, 2012). Several studies in this review have measured EBR under conditions such as watching a video or during an interview, and these studies present a potentially confounded association between DA, EBR, and the population or cognitive measure of interest. In particular studies on atypical populations have examined EBR in various conditions other than primary gaze, e.g. during an interview or watching a video. This methodology might have contributed to variation in results across studies because changes in EBR due to the measurement condition, e.g. during an interview, might have masked differences in EBR as compared to controls. As such we recommend future studies to include assessment of EBR during primary gaze, i.e. in silent rest and looking straight ahead, to provide a reliable baseline measurement for comparison across studies.

Lastly, it is not only important *how* EBR is measured but also *when*, as the circadian rhythm seems to affect DA and therewith EBR. Blink rates are found to be stable between 10 and 17 h (Barbato et al., 2000; Doughty, 2006) but to increase in the evening, paralleling an increase in subjective sleepiness

(Barbato et al., 2000). This finding is consistent with sleep deprivation leading to an increase in both DA and EBR (Barbato et al., 1995, 2007; Crevits, Simons, & Wildenbeest, 2003; Doughty, 2006; Ebert et al., 1996). Because EBR might relate to an individual's subjective sleepiness, perhaps the most reliable estimate of basal DA function and EBR for comparison across studies is obtained during the day rather than the evening or night. Correspondingly, the majority of reviewed studies report measuring EBR only between 9 and 17 h and we highlight the need for future studies to keep accurately reporting the time-of-day for EBR measurements to facilitate between-study comparison.

Future research

We would like to end with several recommendations for future research that hopefully stimulate new lines of research as well as help address unresolved issues and facilitate between-study comparison, some of which have already been mentioned briefly. First of all, drug studies should aim to consider baseline EBR as a determinant of drug-induced change in blink rate. Certain studies present inconsistent results that might be reconciled by distinguishing drug response from low and high baseline blinkers. For example, van der Post et al. (2004) found no change in EBR following administration of drugs known to affect EBR in animals, which might be explained by the finding of Cavanagh et al. (2014) that drug-induced change in EBR can be opposite for low and high baseline blinkers.

Second, we recommend researchers to explicitly report EBR values and associated levels of significance both for baseline conditions and every drug and dose combination they employ, to facilitate between-study comparison. As is evident from this review's tables, it is often not clear which drug and dose combinations yielded significant effects, for example because researchers present their findings only in small figures (plotting drugs and doses against EBR) without clearly flagging all significant changes. Presenting detailed information, e.g. tables that list all drugs, doses, EBR values and significance levels, in addition to figures would allow readers to benefit more from the huge amount of information these studies can provide.

Third, the majority of EBR studies examine only linear correlations or use a median split to distinguish groups of low and high blinkers. Although this is often sufficient to find a distinction in performance, DA and cognitive performance, in particular working memory, often follow a characteristic inverted-u-shaped function (Cools & D'Esposito, 2011). However, the only study so far examining EBR and working memory reported solely linear relations. Such an approach potentially ignores non-linear patterns in the data, leading to loss of valuable information. Indeed, a select few studies have established nonsignificant linear but significant quadratic relations. Specifically, an intermediate EBR might be associated with optimal performance, whereas low and high blink rates are associated with lower performance (Akbari Chermahini & Hommel, 2010, 2012; Dang et al., 2016). Therefore we strongly advise future studies to also consider regression analyses of data instead of only median-split grouping and to report on quadratic relations albeit to confirm their non-significance.

Fourth, to allow unconfounded investigation of EBR and individual differences in cognitive performance, researchers should carefully screen participants not only for neurological and psychiatric conditions known to affect DA but smoking behavior as well. Nicotine, presumably through actions on DA, can affect excitability in the trigeminal complex (Evinger et al., 1993, 1988), which is a proposed neural circuitry for DA modulation of EBR (Kaminer et al., 2011, 2015). Indeed, smoking has been associated with increased blink rates (Klein et al., 1993). Hence, to promote reliable results with a little noise as possible due to smoking behavior, this characteristic ought to either be carefully monitored in participants or be included in the exclusion criteria.

Fifth, an important topic of investigation for future research would be the test-retest reliability of EBR within an individual. After all, if EBR is to be a predictor of individual differences in cognitive function then EBR itself needs to be a stable, reliable measure. Studies investigating the effects of large age ranges (e.g. Zametkin et al., 1979) often present cross-sectional data and thus do not speak to this issue. Although some studies report no significant

differences in baseline EBR between several sessions, few have provided detailed measures of reliability. One recent study explicitly addressing this issue found a high level of consistency in long-term meditators and a healthy control group (Chronbach's alpha of .79 and .85, respectively) in three measurements spaced eight to ten weeks apart (Kruis et al., 2016).

Sixth, although the present review has focused solely on the single, average spontaneous EBR value, there is evidence to suggest *patterns* of blinking might represent a novel informative characteristic. EBR patterns can be based on the time between blinks, i.e. the inter-blink-interval, and have shown to vary between healthy individuals, even in a single experimental condition, while being comparable in terms of average EBR. Three patterns have been proposed: an irregular, a J-type, and a symmetrical pattern (Doughty, 2002). They are characterized, respectively, by longer intervals interspersed with short ones, by progressively longer intervals, and by more constant, regular intervals. So far, no studies have associated these patterns with measures of cognitive performance, even though they might constitute more informative and sensitive markers of individual differences by including both mean of and variance in EBR.

Lastly, whereas studies so far typically calculated an average EBR value across several minutes under constant conditions, a promising novel line of research looks at trial-to-trial changes in EBR to track fluctuations in DA related to ongoing task demands. Two examples of such event-based EBR research are by van Bochove et al. (2013) who showed the Gratton effect (i.e. a conflict-sequence effect) was larger after a blink trial than after a non-blink trial, and by Rac et al. (submitted) who found an association between trial-to-trial EBR and changes in working memory updating and gating demands. These studies suggest EBR can be used to track transient changes in striatal DA activity in response to real-time fluctuations in cognitive demands. As such, event-based EBR might present a unique method of investigating the role of DA in cognitive performance on a trial by trial basis, which is not easily permitted by traditional methods with low temporal resolution such as PET.

Conclusion

To conclude, the present review provides a comprehensive overview or research showing EBR is a useful, easily-accessible marker of DA function with promising utility for a wide variety of research. Although equivocal findings are still present and more systematic research is necessary to resolve these inconsistencies, we strongly encourage future studies to examine the role of EBR in cognitive research.